

ALLERGYWATCH®

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

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Low House Dust Endotoxin Levels Linked to Increased Atopy Risk by Age 2

PREVIOUS studies have suggested that the immune responses of newborn infants may be skewed toward a Th2 response. Regulation of fetal Th1/Th2 balance may require exposure to Th1-stimulating factors in the environment, such as endotoxin. House dust endotoxin levels were compared in European countries with a low vs high prevalence of atopic disease in children.

One hundred fifteen pregnant women from Tartu, Estonia, and 149 from Linköping, Sweden, enrolled in the trial. Children in Tartu have a low prevalence of allergic disease and sensitization during the first 2 years of life, while children in Linköping have a high prevalence. For each participating family, house dust samples were obtained for measurement of endotoxin and allergen levels. Follow-up data were obtained on 108 Estonian and 111 Swedish children, including regular skin prick tests and clinical examination at age 2.

Measured endotoxin levels were twice as high in the Estonian homes as in the Swedish homes. Pet allergen levels were also higher in the Estonian samples. The Swedish children had higher rates of positive skin test results and allergic symptoms, and were also more likely to have a parental history of atopy. Endotoxin level was inversely related to atopic disease and sensitization in Swedish children, though not in Estonian children. Considering endotoxin level as a continuous variable, the odds ratio of atopic symptoms was 0.93—symptom risk decreased by 7% for each 1-unit increase in house dust endotoxin concentration.

These data from two European cities suggest that lower levels of house dust endotoxin are associated with higher rates of atopic sensitization and symptoms in the first 2 years of life. The findings are consistent with the hypothesis that endotoxin or some other Th1-stimulating environmental exposure protects against the development of atopic disease in young children. A related editorial highlights the difficulty of proving a protective effect of a proinflammatory agent such as endotoxin. >>

CONTENTS

- | | |
|--|---|
| 1 Low House Dust Endotoxin Levels Linked to Increased Atopy Risk by Age 2 | 7 Antibiotic Prescribing in the 1990s: Broad-Spectrum Antibiotic Use Is Growing |
| 2 High Rate of GERD, Good Response to Antireflux Treatment in Children With Asthma | 7 Early Budesonide Improves Outcomes in Mild, Persistent Asthma: START Study Results |
| 3 Bilevel Pressure Ventilation Improves Outcomes of Severe Asthma Attacks | 8 Interleukin-4 Receptor Is Increased in Airways of Asthmatic Children |
| 3 Infantile FPIES Induced by Solid Foods: Report of 14 Patients | 8 CAMP Study Finds Normal Growth in Children With Mild to Moderate Asthma |
| 3 Fascinating Observations Related to Penicillin Skin Testing | 9 Celecoxib Doesn't Induce Reactions in Aspirin-Intolerant Asthma Patients |
| 4 Traffic Pollution Linked to Respiratory Symptoms and Atopy in Children | 9 Study Explores Mechanisms of Mepolizumab's Antieosinophil Effect |
| 5 "Hot Tub Lung"—Mycobacterial Lung Disease in an Immunocompetent Patient | 10 Role of Neutrophils and IL-8 Studied in Persistent Asthma |
| 5 Sedative Effect of Diphenhydramine: Meta-Analysis | 10 Montelukast Add-on Therapy Improves Inflammatory Markers But Not Lung Function |
| 6 Pneumococcal Vaccine Doesn't Reduce Pneumonia Risk in Older Adults | 11 Survey Finds Low Rate of Needlestick Injuries in Allergy Practice |
| 6 Maternal Asthma Modifies Impact of Day Care Attendance on Childhood Asthma | 11 Evidence of Tolerance to β -Agonists Is Increased During Bronchoconstriction |
| | 12 REVIEWS OF NOTE |

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- American Journal of Respiratory and Critical Care Medicine
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COMMENT: This study compares two European cities: one with a low prevalence of atopy and the other with a high prevalence of atopy. The mean house dust endotoxin levels were dramatically different, supporting the hypothesis that endotoxin plays a protective role against the development of atopic diseases by diverting the focus of the immune system toward a Th1 response. As the accompanying editorial points out, the cause-and-effect relationship between low endotoxin levels and the development of respiratory disease has not yet been definitively proven.

S. A. T.

Böttcher MG, Björkstén B, Gustafson S, et al: Endotoxin levels in Estonian and Swedish house dust and atopy in infancy. *Clin Exp Allergy* 33:295-300, 2003; and Niven R: The endotoxin paradigm: a note of caution. *Clin Exp Allergy* 33:273-276, 2003. ♦♦

High Rate of GERD, Good Response to Antireflux Treatment in Children With Asthma

ALTHOUGH some relationship between gastroesophageal reflux disease (GERD) and asthma is apparent, the nature of the association is unclear. Studies in adults have found that treatment for GERD can lead to improvement in asthma. The relationship between GERD and asthma in children was assessed, including the response to antireflux treatment.

The study included 46 children who had moderate, persistent asthma for longer than 2 years and were receiving treatment with bronchodilators, inhaled corticosteroids, and leukotriene antagonists. There were 27 boys and 19 girls, age range 5.0 to 10.5 years. All underwent 24-hour esophageal pH monitoring. Based on a distal esophageal pH of less than 4 for more than 5% of monitoring time, 27 patients (59%) were diagnosed as having GERD. All of these 27 patients received treatment for GERD: medical in 18 patients and surgical in 9. Of the 19 patients without pH probe evidence of GERD, 8 received medical antireflux treatment.

In the patients with confirmed GERD, antireflux therapy was followed by significant reductions in the use of short- and long-acting bronchodilators and inhaled corticosteroids. Use of asthma medication also decreased in 2 of the 8 patients receiving antireflux medication without a diagnosis of GERD, compared with none of the 11 patients receiving no treatment. After 12 months of observation, none of the patients with pH probe evidence of GERD were still using long-acting bronchodilators, while just 11% still required inhaled corticosteroids.

In this study, most children with persistent moderate asthma had pH probe evidence of GERD. For this group, medical or surgical antireflux treatment significantly reduces the need for asthma medications. The study has several key limitations and raises many new questions, particularly regarding the role of antireflux treatment. However, it is one of the first to address the relationship between GERD and asthma in children.

COMMENT: Gastroesophageal reflux disease may aggravate symptoms in many patients with asthma, despite the absence of classic reflux symptoms. This has been a difficult relationship to investigate and requires several months of evaluation in clinical studies. These investigators, in a "real life" trial, look at older children with persistent asthma and the association of GERD. Almost 60% of these children had abnormal pH probe studies and underwent medical or surgical treatment for gastroesophageal reflux. All the patients treated for GERD had over a 50% reduction in asthma medications over a 1-year period—even 25% of the empirically treated group improved. Gastroesophageal reflux disease should be at the top of our list to investigate in children and adults with difficult-to-control asthma.

A. L. L.

Khoshoo V, Le T, Haydel RM Jr, et al: Role of gastroesophageal reflux in older children with persistent asthma. *Chest* 123:1008-1010, 2003. ♦♦

Bilevel Pressure Ventilation Improves Outcomes of Severe Asthma Attacks

NONINVASIVE ventilation is effective for patients with acute respiratory failure, but its potential benefits in patients with acute asthma remain unclear. The use of nasal bilevel pressure ventilation (BPV) for severe asthma attacks was evaluated in a pilot study.

Of a series of 124 patients with severe asthma attacks seen in a university hospital emergency department, 30 were enrolled in the randomized trial. All patients received conventional treatment: nebulized salbutamol and ipratropium plus intravenous corticosteroids as indicated. Patients in the intervention group received 3 hours of ventilatory support with BPV at predetermined inspiratory and expiratory pressures, while those in the control group received sham BPV. The main outcome measure was improvement in FEV₁ from baseline.

Baseline characteristics were similar between groups. An FEV₁ increase of at least 50% was achieved in 80% of patients receiving BPV, compared with 20% of controls. Mean increases in FEV₁ were 53.5% vs 28.5%, respectively. Intention-to-treat data in 33 patients found a hospitalization rate of 17.6% in patients receiving active BPV, compared with 62.5% in those receiving sham BPV.

Adding BPV to conventional treatment may have important benefits for patients with severe asthma attacks, this pilot study suggests. Active BPV is associated with greater improvement in lung function, faster relief of the asthmatic attack, and a substantial reduction in hospitalization rate.

COMMENT: Nasal BPV is a noninvasive, relatively comfortable form of ventilatory support that has previously been shown to be efficacious in selected patients with pulmonary edema or COPD exacerbations. This pilot study reported impressive effects of BPV on spirometry and hospitalization rate in subjects presenting to the emergency department with acute asthma. If these results can be replicated in a larger, multicenter study, BPV could become a more widely used treatment modality.

S. A. T.

Soroksky A, Stav D, Shpirer I: A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack.

Chest 123:1018-1025, 2003. ♦♦

Infantile FPIES Induced by Solid Foods: Report of 14 Patients

INFANTS with food protein-induced enterocolitis syndrome (FPIES) have serious vomiting and diarrhea, most often induced by cow's milk or soy-based formula. Despite some case reports, there are relatively few data on solid food proteins as triggers of FPIES. A series of 14 infants with FPIEs caused by solid foods is reported.

The infants were referred over a 5-year period. They had typical FPIES symptoms, including profuse vomiting, diarrhea, melena, and hypotension within 1 to 3 hours after food ingestion. In 71% of patients, symptoms were severe enough to lead to emergency department evaluation or hospitalization; 57% developed shock requiring emergency medications or intravenous fluids. Based on food challenges, the implicated foods included grains, ie, rice, oats, and barley; vegetables, including sweet potato, squash, string beans, and peas; and poultry, ie, chicken and turkey. Skin tests to these foods were negative, although 3 patients developed food-specific IgE antibodies.

The findings were compared with those of 30 infants with typical FPIES related to cow's milk or soy. In the combined group of 44 infants, 48% reacted to more than 1 food protein. For those with solid food- or soy-related FPIES, the rate of multiple food sensitivities was nearly 80%. Reactions occurred only when the offending food was fed to the infant directly, never when the mother ingested the food before breast-feeding. Median age at diagnosis was 5.5 months for infants reacting to solid foods, compared with 1 month for those reacting to cow's milk or soy. Infants reacting to solid foods were breast-fed longer than those reacting to cow's milk or soy.

This is the first reported series of infants with FPIES related to solid food proteins. Oats appear to be the most frequently involved food, although other grains, vegetables, and poultry are implicated as well. Solid food-related FPIES tends to be severe, and diagnosis may be delayed. Affected infants have a high rate of multiple food hypersensitivities; breast-feeding may have a protective effect in infants predisposed to FPIES.

COMMENT: Food protein-induced enteropathies are primarily caused by cow's milk and soy. These reactions are cell mediated, often slow in onset, and produce variable mucosal damage. Thus the diagnosis is not easy to establish, often requiring serial GI biopsies with withdrawal and rechallenge of the offending food(s). These distinguished investigators add several solid foods to worry about as well. Interestingly, these infants with solid food protein enteropathies often have a history of hypersensitivity to cow's milk and soy formulas. As with many other conditions, breast-feeding appears to have some protective effect against such enteropathies.

A. L. L.

Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH: Food protein-induced enterocolitis syndrome caused by solid food proteins.

Pediatrics 111:829-835, 2003. ♦♦

Fascinating Observations Related to Penicillin Skin Testing

PENICILLIN skin testing is highly predictive of a patient's ability to tolerate penicillin treatment without allergic reactions, although there is concern about the length of time that such results remain valid. Some studies have suggested that patients may▶▶

become resensitized after penicillin treatment; however, the sensitizing potential of the skin test itself is unknown. The rate of sensitization caused by penicillin skin testing was assessed.

Penicillin skin testing was performed in 329 adult volunteers. Seventy-two subjects had a history of previous reactions to β -lactam drugs, of whom 14% had positive results on initial skin testing. The overall rate of positive results on the initial skin test was 7%. Factors associated with a positive result were asthma, female sex, and atopy.

One month later, skin testing was repeated in 239 patients with an initially negative result. The results were now positive in 6 subjects, a rate of 2.5%. Factors associated with conversion from a negative to a positive result were female sex, atopy, and food allergy. There was also a trend toward recent penicillin use among patients whose tests became positive.

Of subjects with an initially negative penicillin skin test result, 2.5% will convert to a positive result when retested 1 month later. Certain factors may increase the likelihood of this finding. The findings suggest that the penicillin skin test itself has the potential to cause sensitization; it is unknown whether the subjects in this study were clinically sensitized.

COMMENT: *This study addresses a question that has long challenged allergists: Can allergy testing cause sensitization? The results indicate that a small proportion of patients tested to penicillin 1 month apart may indeed convert to positive skin tests. These findings should not deter clinicians from penicillin testing in the appropriate clinical setting.*

A. M.

Nugent JS, Quinn JM, McGrath CM, et al: Determination of the incidence of sensitization after penicillin skin testing.

Ann Allergy Asthma Immunol 90:398-403, 2003. ♦♦

BECAUSE of concerns about resensitization, patients rarely undergo penicillin skin testing before they require penicillin therapy. Few studies have looked at the rate of penicillin reactions or resensitization among patients with a positive history of penicillin allergy but a negative skin test result. The long-term risk of reactions to oral penicillins was assessed in a large group of such penicillin "allergic" but skin-test-negative patients.

The retrospective study identified 568 adult patients who had a negative result on penicillin skin testing in advance of need and went on to receive one or more courses of penicillin during routine clinical care. During a mean follow-up of 4.26 years, these patients received a mean 3.94 courses of oral penicillin. The type, severity, and frequency of adverse reactions were assessed.

In a total of 2,236 courses of penicillin treatment, 71 adverse reactions occurred, a rate of 3.2%. Although 4 episodes were reported as "anaphylaxis," none started within 1 hour after treatment, caused systemic symptoms, or required more than antihistamine or steroid

therapy. The mean number of courses of penicillin treatment since the initial negative skin test result was 4.75 in patients who had an adverse reaction and 3.83 in those who did not. Of patients who had an adverse reaction to their first course of penicillin after the negative skin test, one-third went on to receive further courses with no reaction. When skin tests were repeated in 33 patients, just 1 had a positive result.

The findings support the safety of skin testing for penicillin allergy in advance of need. The risk of resensitization appears very low, as does the rate of serious adverse reactions among patients with negative skin test results. In this series, the rate of true IgE-mediated penicillin allergy—defined as a significant adverse drug reaction and a positive skin test—is just 0.38%.

COMMENT: *The Kaiser group in San Diego analyzed data from a group of 1,246 patients who were skin-test negative to penicillin over a mean of 4+ years. Using pharmacy records, the investigators identified 568 patients who received penicillin for therapy. Although 65 (11.4%) did have reactions after penicillin, they were not considered to be anaphylaxis. The overall reaction rate was only 3.2%, although most reactions were not considered to be IgE- or T-cell-mediated. Identification of patients who truly have IgE-mediated risk of anaphylaxis is our major concern. It appears that a negative penicillin skin test with oral challenge should be reassuring, implying a minimal risk of resensitization.*

S. M. F.

Macy E, Mangat R, Burchette RJ: Penicillin skin testing in advance of need: multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins

J Allergy Clin Immunol 111:1111-1115, 2003. ♦♦

Traffic Pollution Linked to Respiratory Symptoms and Atopy in Children

AIR pollution is a possible contributor to the rising rates of allergic respiratory disease. Automobile traffic is a major source of air pollution in cities. Exposure to automobile emissions appears to adversely affect respiratory symptoms and lung function in children, although its effect on allergy remains unclear. The relationship between traffic pollution and asthma and allergic disease in children was analyzed.

A random sample of 7,509 schoolchildren in Munich, Germany, were studied, including a questionnaire regarding respiratory symptoms, skin prick testing to common aeroallergens, specific IgE measurements, and lung function studies. Data on traffic counts in the area of the children's homes were used to estimate exposure to traffic pollutants: soot, benzene, and nitrogen dioxide.

Children living near busy streets were more likely to be of low socioeconomic status. Total traffic count was significantly related to the symptoms of cough, current asthma, and wheezing, with evidence of a dose-response effect. On stratification by skin prick test results, ►►

these associations were significant only for children with atopy. For children exposed to environmental tobacco smoke, traffic volume was associated with asthma and positive skin test results. Asthma was associated with soot and benzene levels, wheezing with benzene and nitrogen dioxide, and cough with all three pollutants. None of the pollutants was significantly related to lung function studies or bronchial hyperresponsiveness.

Living in areas with high vehicle traffic counts is significantly associated with respiratory symptoms in children, this population-based study suggests. Estimated exposure to pollutant levels is also related to respiratory symptoms, although the nature of this association is less clear. Children living in high-traffic areas tend to be of lower socioeconomic status, making it difficult to assess the direct effects of exposure to traffic pollution.

COMMENT: Another component of the gene-environment interaction leading to allergy and asthma is external environmental pollution, particularly from urban traffic pollutants. This study looked at a fairly large number of children (7,500+) in terms of their exposure to soot, benzene, and nitrogen dioxide from urban traffic exposure. There was a direct effect on established asthma, cough, and wheeze. When tobacco smoke exposure was factored in, a further association with positive skin tests was noted. However, pollutant exposure alone was not associated with allergic sensitization. The authors note that there are further psychosocial differences in children who live close to major roads vs those who do not, which may influence the results. Regardless, this paper further supports the immune-altering effects of pollution and cigarette smoke in the urban-associated allergy-asthma picture.

G. D. M.

Nicolai T, Carr D, Weiland SK, et al: Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children.

Eur Respir J 21:956-963, 2003.

◆◆

"Hot Tub Lung" -- Mycobacterial Lung Disease in an Immunocompetent Patient

PULMONARY disease caused by *Mycobacterium avium* complex (MAC) may take a wide range of forms, but most often occurs in patients with AIDS or older adults with underlying pulmonary disease or other predisposing conditions. Recent reports have described MAC pulmonary illness associated with hot tub use by previously healthy people.

A 49-year-old woman was hospitalized with fever, chills, chest radiographic abnormalities, and a 3-week history of headache and upper respiratory symptoms. Her symptoms grew worse despite treatment with erythromycin and levofloxacin. Chest radiographs showed bilateral interstitial and alveolar infiltrates. The patient was started on intravenous antibiotics and her condition improved, though sputum and other tests identified no cause of her infection. However, 1 week after discharge, her respiratory symptoms returned, along with gas-

trointestinal symptoms.

Previous sputum specimens revealed acid-fast bacilli that eventually proved to be MAC. Stool samples were positive for *Clostridium difficile*, for which the patient was started on metronidazole therapy. The clinical findings, together with histopathologic examination of a transbronchial lung biopsy, were consistent with hypersensitivity pneumonitis. The patient had recently bought a hot tub, and samples from the tub water and filter were strongly positive for MAC. After she stopped using the hot tub, her condition improved rapidly, with no steroid or antimycobacterial treatment. By 2 months' follow-up, she had recovered completely.

Another case of "hot tub lung" caused by MAC in a previously healthy patient is reported. These cases may appear as an infection, hypersensitivity pneumonitis, or both. Patients should be advised of the risks of using a hot tub, and urged to keep the water and filter clean.

COMMENT: Pulmonary involvement by MAC has historically afflicted immunocompromised individuals or patients with pre-existing lung pathology. A number of recent cases have occurred in healthy patients who have used hot tubs. In these instances, the histopathologic findings suggest a form of hypersensitivity pneumonitis. Clinicians should be aware that this is a potential risk associated with hot tub use.

E. J. B.

Cappelluti E, Fraire AE, Schaefer OP: A case of "hot tub lung" due to *Mycobacterium avium* complex in an immunocompetent host.

Arch Intern Med 163:845-848, 2003.

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Sedative Effect of Diphenhydramine: Meta-Analysis

DIPHENHYDRAMINE and other first-generation antihistamines are still widely used, despite their potential to cause sedation. Diphenhydramine in particular is commonly used as a control to demonstrate the relative lack of sedation caused by second-generation antihistamines. Published data were analyzed to compare the sedative effects of diphenhydramine with those of placebo and second-generation antihistamines.

The investigators performed a literature search to identify blinded, randomized clinical trials assessing the sedative effects of diphenhydramine vs placebo or second-generation antihistamines. All studies included objective assessments of alertness and psychomotor performance, including tests of attention, memory, reaction time, and eye-hand coordination, and evoked brain potentials.

A total of 18 studies were included in the meta-analysis. Studies comparing diphenhydramine with placebo suggested a moderate but variable sedative effect of diphenhydramine. The studies of second-generation antihistamines included several different medications, such as acrivastine, astemizole, cetirizine, fexofenadine, and loratadine. As with placebo, the sedative effect of diphenhydramine was moderate but variable and not consistently present. On some performance tests, diphenhydramine actually seemed less sedating >>>

than placebo or second-generation antihistamines; the nonsedating antihistamines had a mild sedative effect compared with placebo. The data were insufficient to analyze the impact of potential influencing variables, such as funding source, dose, duration of treatment, and symptom severity. Most studies used a 50 mg dose of diphenhydramine.

The available data suggest that diphenhydramine has a significant sedating effect. However, the magnitude of this effect is relatively small and it is not consistently demonstrated. The findings raise questions about the putative difference between "sedating" and "nonsedating" antihistamines, including the effect of the usual 25 mg dose of diphenhydramine and the role of impairment caused by allergic rhinitis itself.

COMMENT: *Some controversies just never die. How sedating are older antihistamines relative to the newer "nonsedating" antihistamines? Is it axiomatic that diphenhydramine is sedating? This meta-analysis looks at 18 blinded and controlled studies and finds that diphenhydramine has not been consistently shown to be sedating, even at 50 mg. Few studies have even looked at the common over-the-counter dose of 25 mg. It also finds that the nonsedating antihistamines are more sedating than placebo in their usual doses. The authors conclude that "a clear and consistent distinction between sedating and nonsedating antihistamines does not exist." Before reaching an unassailable position on the topic, further study of this data set is recommended.*

R. J. M.
Bender BG, Berning S, Dudden R, et al: Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. *J Allergy Clin Immunol* 111:770-776, 2003. ♦♦

Pneumococcal Vaccine Doesn't Reduce Pneumonia Risk in Older Adults

STREPTOCOCCUS pneumoniae is the most frequent causative pathogen of community-acquired pneumonia in the elderly. Despite several studies, it remains unclear whether the 23-valent pneumococcal polysaccharide vaccine can reduce the risk of pneumonia in older adults. The pneumococcal polysaccharide vaccine's effects on the rate of community-acquired bacteremia were examined in a large, population-based, retrospective cohort study.

The analysis included 47,365 HMO enrollees aged 65 years or older, with a total follow-up of 127,180 person-years. The effects of pneumococcal vaccination on community-acquired pneumonia requiring hospitalization, outpatient pneumonia, and pneumococcal bacteremia were assessed.

Of the total follow-up, two-thirds occurred after pneumococcal vaccination. Hospitalization for community-acquired pneumonia occurred in 1,428 subjects, outpatient pneumonia in 3,061, and pneumococcal bacteremia in 61. The rate of pneumococcal bacteremia was significantly reduced in vaccinated patients, hazard ratio 0.56. In contrast, pneumococcal vaccination was associated with a small but significant increase in the

risk of hospitalization for pneumonia, hazard ratio 1.14. Receiving the vaccine did not significantly affect the overall risk of community-acquired pneumonia, requiring hospitalization or not.

The results show a 44% reduction in the risk of pneumococcal bacteremia in elderly patients receiving the 23-valent pneumococcal polysaccharide vaccine. However, the risk of community-acquired pneumonia is unaffected, while the rate of pneumonia requiring hospitalization may actually be increased. New approaches are needed to prevent pneumococcal pneumonia that is not accompanied by bacteremia, which is the more common presentation in older adults.

COMMENT: *It is disputed whether the 23-valent pneumococcal polysaccharide vaccine prevents adult community-acquired pneumonia, of which S. pneumoniae is the most common pathogen. This study evaluated the records of over 47,000 elderly patients of a health care system over a 3-year period. Those who had received the vaccine had a significant reduction in risk of pneumococcal bacteremia, but there was no reduction in the occurrence of outpatient/community-acquired noninvasive pneumonia.*

R. J. M.

Jackson LA, Neuzil KM, Yu O, et al, for the Vaccine Safety Datalink: Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med* 348:1747-1755, 2003. ♦♦

Maternal Asthma Modifies Impact of Day Care Attendance on Childhood Asthma

ONE explanation advanced for the rising incidence of asthma is a reduction in young children's exposure to other children and in the risk of infections. Previous studies have suggested that young children attending day care have a lower rate of asthma by the time they reach school age. The effects of maternal history of asthma on this relationship were studied.

The analysis included 453 Boston-area children with a parental history of atopy, followed up from birth through age 6. Of these, 238 attended day care during the first year of life, most often in a home day care setting. Early day care attendance was associated with a significant reduction in the risk of eczema, odds ratio (OR) 0.3.

However, day care attendance was associated with a reduced risk of asthma only for the 322 children whose mothers did not have asthma. For children with a maternal history of asthma, early day care was linked to an increased risk of wheezing by age 6. Risk of allergic rhinitis was unaffected by day care attendance, while paternal history of asthma did not appear to affect the children's atopic disease outcomes.

Early day care attendance does not reduce the risk of asthma for the children of mothers with asthma. In contrast, for children with a family history of atopy but no maternal history of asthma, early day care attendance is associated with a lower rate of later asthma and wheezing. The mechanism by which maternal history of >>>

asthma affects the association between day care attendance and childhood asthma risk may reflect genetic factors or environmental exposures shared by the mother and child.

COMMENT: *The questions regarding gene-environmental interactions in the development of allergy and asthma are increasingly well-defined. The continuing debate as to the clinical relevance of the hygiene hypothesis is now being focused on more specific questions. One such is the effects of early day care exposure (first year of life) on subsequent development of asthma in children with and without maternal history. This study demonstrated a protective effect of day care exposure on asthma risk only in 6-year-old children without a maternal history of asthma. Indeed, children of mothers with asthma actually had an increased risk of wheezing in the first 6 years of life. These data further demonstrate the validity of gene-environmental interactions leading to or protecting against asthma, but they also show the fallacy of an overly simplistic interpretation of the hygiene hypothesis paradigm.*

G. D. M.

Celedón JC, Wright RJ, Litonjua AA, et al: Day care attendance in early life, maternal history of asthma, and asthma at the age of 6 years.

Am J Respir Crit Care Med 167:1239-1243, 2003. ♦♦

Antibiotic Prescribing in the 1990s: Broad-Spectrum Antibiotic Use Is Growing

THE growing problem of antimicrobial resistance has important implications for outpatient antibiotic use. National Ambulatory Medical Care Survey data were used to assess trends in antibiotic prescribing throughout the 1990s.

The analysis divided survey data into three periods: 1991-92, 1994-95, and 1998-99. With patient weighting, the data could be extrapolated to represent about 650 million annual U.S. community outpatient visits. The study focused on patterns in prescribing of broad-spectrum antibiotics: azithromycin and clarithromycin, quinolones, amoxicillin-clavulanate, and second- and third-generation cephalosporins.

Across the periods studied, the percentage of visits at which an antibiotic was prescribed decreased from 13% to 10% for adults and from 33% to 22% for children. Total annual number of antibiotic prescriptions decreased from 230 to 190 million. By diagnosis, prescribing for colds, unspecified upper respiratory infections, and pharyngitis decreased for both adults and children and for acute bronchitis in adults.

However, as a proportion of all antibiotics prescribed, the use of broad-spectrum antibiotics in adults increased from about one-fourth to about one-half. This was so for all categories of broad-spectrum antibiotics except the second- and third-generation cephalosporins. Prescribing of broad-spectrum antibiotics increased across age groups and across diagnoses.

By 1998-99, most prescriptions for broad-spectrum antibiotics were for nonpneumonic acute respiratory infections: 54% in adults and 77% in children. Substantial percentages of prescriptions for broad-spectrum antibiotics were given for indications such as colds, unspecified upper respiratory infections, and sinusitis. In children, 27% of prescriptions were given for otitis media.

Antibiotic prescribing for outpatients decreased significantly during the 1990s, especially among children and in conditions for which these drugs are of limited value. However, when antibiotics are prescribed, they are increasingly likely to be broad-spectrum antibiotics, even when the use of such drugs may not be justified. Continued increases in use of broad-spectrum antibiotics may lead to new problems with antibiotic resistance.

COMMENT: *The problem of increasing bacterial resistance is a major concern. The dilemma we face as specialists is that we care for patients in whom prior treatment has failed; who have persistent symptoms; and who have a suspected, but unproven, bacterial component to their disease. Is it preferable to obtain clinical samples for culture; to use the newest, broadest empirical antibiotic or risk treatment failure and increase resistance; or to use higher dosages of anti-inflammatory therapy and withhold antibiotics? These decisions will become more challenging with the pending introduction of the ketolide family of antibiotics. The challenge grows.*

D. K. L.

Steinman MA, Gonzales R, Linder HA, Landefeld CS: Changing use of antibiotics in community-based outpatient practice, 1991-1999.

Ann Intern Med 138:525-533, 2003.

Early Budesonide Improves Outcomes in Mild, Persistent Asthma: START Study Results

INHALED glucocorticosteroids are recommended for patients with persistent asthma, and may provide better outcomes if started within 2 years after the start of symptoms. However, the long-term effects of early treatment for patients with mild, persistent asthma of recent onset are unknown. The "inhaled steroid treatment as regular therapy in early asthma" (START) study evaluated the benefits of early budesonide therapy in this group of patients.

The randomized, controlled trial included 7,241 patients who had mild, persistent asthma for less than 2 years and had received no regular glucocorticosteroid therapy. The patients, ranging in age from 5 to 66 years, were drawn from 32 countries. They were randomized to receive once-daily budesonide or placebo via dry-powder inhaler, in addition to their usual asthma treatment. Budesonide dose was 400 µg/d, or 200 µg/d for children under age 11. The main study endpoint was time to first severe asthma-related event. The ►►

study was funded by a pharmaceutical company.

The final analysis included 3,597 patients assigned to budesonide and 3,568 assigned to placebo. On intention-to-treat analysis, budesonide was associated with significant reduction in the risk of an initial severe asthma-related event, hazard ratio 0.56 for all patients. A similar risk reduction was noted for the 60% of patients who had a prebronchodilator FEV₁ over 80% and were not receiving glucocorticosteroid therapy at enrollment. Patients in the budesonide group also required fewer courses of systemic corticosteroids and had more symptom-free days. Budesonide was associated with a significant increase in postbronchodilator FEV₁ percent predicted: by 1.48% at 1 year and 0.88% at 3 years. Children using the inhaled corticosteroid had a modest but significant reduction in growth, mean 1.34 cm at 3 years.

For patients with mild, persistent asthma, early treatment with once-daily, low-dose budesonide appears to reduce the risk of severe asthma exacerbations at 3 years' follow-up. Other clinical outcomes and lung function measurements are also improved with budesonide, although the difference vs placebo may lessen over time. The results support recommendations for the use of inhaled glucocorticosteroids for mild, persistent asthma.

COMMENT: *This large study reports on patients with mild persistent asthma for less than 2 years who were not taking a corticosteroid regularly. They were given low-dose budesonide or placebo for 3 years. The budesonide group had a reduction in exacerbations and need for systemic steroids, along with an improvement in asthma control. The study's strengths are its large size and generalizable findings. Weaknesses include the large number of dropouts and allowing 5% of subjects to be using an inhaled steroid on entry. The study also provides data on the natural history of asthma--FEV₁ values tended to converge after 3 years, arguing against a disease-modifying effect.*

E. J. B.

Pauwels RA, Pedersen S, Busse WW, et al, on behalf of the START Investigators Group: Early intervention with budesonide in mild persistent asthma: a randomized, double-blind trial.

Lancet 361:1071-1076, 2003. ◆◆

Interleukin-4 Receptor Is Increased in Airways of Asthmatic Children

THE Th2-type cytokine interleukin-4 (IL-4) is involved in immunoglobulin isotype switching from IgG to IgE, as well as eosinophil adhesion to endothelium. Levels of IL-4 are increased in patients with asthma and other allergic diseases. The IL-4 soluble receptor α (IL-4sR α) appears to act as a circulating IL-4 inhibitor, binding to the active site of IL-4. Levels of IL-4 and IL-4sR α were measured in bronchoalveolar lavage (BAL) fluid of children with and without asthma.

The study included three groups of children undergoing elective surgery at a children's hospital: 55 with atopic asthma, 34 with atopy but without asthma, and 27

nonatopic children. Each child underwent nonbronchoscopic BAL, with sensitive assays used to measure IL-4 and IL-4sR α in the BAL fluid. The ratio of IL-4sR α to IL-4 was compared in children with vs without asthma.

Mean IL-4 concentration was 0.13 pg/mL in all three groups. The children with atopic asthma had a higher mean IL-4sR α level than the atopic controls, 6.4 vs 5.0 pg/mL. However, the receptor level in asthmatic children was not significantly different from that in nonatopic controls, mean 5.2 pg/mL. Within the asthma group, both measures were similar for children with persistent vs episodic asthma.

Unexpectedly, this study finds a higher level of IL-4sR α in BAL fluid of children with stable asthma compared with nonatopic controls. The significance of this finding is unclear--release of IL-4sR α by airway inflammatory cells may serve as a limiting factor on IL-4 activity, or the excess of IL-4sR α may prolong the duration of action of IL-4 in the atopic airway.

COMMENT: *This study furthers our understanding of the central role of IL-4 in allergic inflammation. The authors point out that soluble IL-4 receptors in BAL fluid may promote further allergic inflammation in asthmatic airways, but that further work will be necessary to validate these findings. Is it possible that the proposed treatment of asthma by inhaled soluble IL-4 receptors may be counterproductive?*

A. M.

Fitch PS, Brown V, Schock BC, et al: Interleukin-4 and interleukin-4 soluble receptor α levels in bronchoalveolar lavage from children with asthma.

Ann Allergy Asthma Immunol 90:429-433, 2003. ◆◆

CAMP Study Finds Normal Growth in Children With Mild to Moderate Asthma

CURRENT treatment guidelines call for inhaled corticosteroid therapy for children with persistent, mild to moderate asthma. Although corticosteroids may adversely affect growth, the same may be true for persistent, uncontrolled asthma. The growth effects of mild to moderate persistent asthma and its treatment were assessed in a large group of children enrolled in a randomized trial of asthma treatment.

The cross-sectional study included data on 1,041 children with mild to moderate persistent asthma. The children were 5 to 12 years of age; 40% were girls and 32% were of ethnic/racial minorities. Data on asthma severity and history of asthma treatment were compared with measures of growth and development, including linear growth as measured by Harpenden stadiometry; and bone mineral density (BMD) of the lumbar spine, measured by dual-energy radiography absorptiometry.

In the sample overall, mean height percentile was 56.0% while mean BMD was 0.65 g/cm². Measures of asthma severity were unrelated to either linear growth or BMD. Past corticosteroid treatment also had no apparent effect on growth or BMD.



This large study of children with mild to moderate asthma shows no effect of asthma severity or treatment on the children's growth and development. This is so despite the presence of asthma severe enough to reduce lung function, often present for several years. Children with mild to moderate persistent asthma do not appear to be at risk of impaired growth.

COMMENT: Often "negative studies" (those which do not demonstrate a significant difference from normal) are not interesting to the reader. This study, however, which demonstrates that U.S. children who have had asthma for many years have normal growth and BMD, is worth reading. Some of the important aspects of the study include its large (1,000+), diverse group of subjects, all of whom apparently had good nutrition; and the lack of change from normal in growth/BMD with variation in asthma severity or previous oral/inhaled corticosteroid use. This new information does not wholly negate previous (smaller) studies showing that severe, poorly controlled asthma can affect growth. It is reassuring, however, that the "usual" U.S. child with moderate asthma is not likely to grow up short!

J. A. A.

Kelly HW, Strunk RC, Donithan M, et al, for the Childhood Asthma Management Program (CAMP): Growth and bone density in children with mild-moderate asthma: a cross-sectional study in children entering the Childhood Asthma Management Program (CAMP). *J Pediatr* 142:286-291, 2003. ♦♦

Celecoxib Doesn't Induce Reactions in Aspirin-Intolerant Asthma Patients

ASPIRIN-intolerant asthma (AIA) is associated with bronchoconstriction and other adverse reactions to conventional nonsteroidal anti-inflammatory drugs (NSAIDs), which nonselectively inhibit cyclo-oxygenase (COX). It is unclear whether patients with AIA can tolerate the newer COX-2 selective NSAIDs, such as celecoxib. The results of celecoxib challenge studies in patients with AIA are reported.

The study included 33 patients with typical AIA and a positive response to inhaled or oral aspirin. On two study days 1 week apart, the subjects underwent double-blind challenges with placebo and celecoxib, with celecoxib given in increasing doses of 10, 30, and 100 mg in suspension. Afterward, all subjects underwent an open challenge with celecoxib 400 mg, corresponding to the maximal recommended daily dose of this medication.

The double-blind challenges caused no significant changes in lung function or nasal symptom scores and no extrapulmonary responses. Neither was there any change in urinary excretion of leukotriene E₄, a biochemical marker of aspirin intolerance.

The COX-2 inhibitor celecoxib does not appear to cause bronchoconstriction or other adverse effects in patients with well-characterized AIA. There is also no biochemical evidence of an intolerance reaction. The findings suggest that the intolerance reactions in AIA are related to inhibition of COX-1, not COX-2. Larger stud-

ies will be needed to establish the safety of COX-2 inhibitor treatment in patients with AIA.

COMMENT: Three research centers from three countries combine their data to report results of oral challenges with increasing doses of celecoxib in documented aspirin-sensitive asthmatics. Not only were there no clinical reactions to the celecoxib challenges, there was also no change in urinary leukotriene E₄. The authors suggest that COX-2 inhibitors may be safe for aspirin-sensitive asthmatics, but caution that supervised challenges would be appropriate until larger, longer-term studies are reported.

S. M. F.

Gyllfors P, Bochenek G, Overholt J, et al: Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgesic drug celecoxib.

J Allergy Clin Immunol 111:1116-1126, 2003. ♦♦

Study Explores Mechanisms of Mepolizumab's Antieosinophil Effect

INTERLEUKIN-5 (IL-5) plays a role in the development of eosinophils from CD34+ progenitor cells. Patients with atopic asthma show increased numbers of eosinophils and progenitor cells not only in their bone marrow but also within the bronchial mucosa. The anti-IL-5 antibody mepolizumab was used to study the involvement of IL-5 in eosinophil development in both sites.

The study used bronchial biopsy and bone marrow samples from 24 mildly asthmatic subjects randomized to receive mepolizumab or placebo as part of a clinical study. Mepolizumab was associated with a mean 37% reduction in eosinophil myelocytes, as well as a 44% reduction in metamyelocytes within the bone marrow, compared with placebo. This was despite the lack of difference in total number of CD34+ cells in blood or bone marrow. The percentage of CD34+ cells expressing the IL-5 receptor α (IL-5R α) chain in blood and bone marrow was also unchanged.

Mepolizumab treatment reduced the number of CD34+/IL-5R α mRNA+ cells in the bronchial mucosa. However, this difference was not significant, compared with the placebo group.

Anti-IL-5 therapy with mepolizumab reduces terminal differentiation of eosinophils in the bone marrow of asthmatic patients, but had no significant effect on the number of early eosinophil progenitor cells. The results are consistent with the hypothesis that anti-IL-5 blocks all stages of eosinophil maturation occurring after the CD34+ cell stage; however, other explanations are possible as well. The finding that mepolizumab lowers CD34+/IL-5R α mRNA+ cell numbers in the airway supports a role of IL-5 in local eosinophil development in asthma.

COMMENT: As new, more selective monoclonal antibodies are developed, it is important to understand their specific effects. Using anti-IL-5, these ►►

researchers were able to demonstrate a significant reduction of terminal differentiation-type eosinophils from the bone marrow and bronchial mucosa of allergic asthmatics. There was no reduction in early progenitor CD34+ and CD34+/IL-5R α mRNA+ cells. This shows that IL-5 plays an important role in eosinophil differentiation, but the persistence of CD34+ cells indicates there may be a redundancy of cytokine fusion in eosinophil development. No clinical benefit has yet been demonstrated for anti-IL-5, but who can predict what will be found as our understanding of eosinophil physiology is expanded? Further studies will be required to determine the relevance of these data.

S. M. F.

Menzies-Gow A, Flood-Page P, Sehmi R, et al: Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics.

J Allergy Clin Immunol 111:714-719, 2003. ◆◆

Role of Neutrophils and IL-8 Studied in Persistent Asthma

THE eosinophil appears to be an important effector cell in asthma, but the role of neutrophils and other granulocytes remains uncertain. Long-acting β_2 -agonists show evidence of a neutrophil-stabilizing effect. The effects of a long-acting β_2 -agonist on neutrophils, the neutrophil-related chemokine interleukin-8 (IL-8), and the activation marker myeloperoxidase (MPO) were studied in patients with persistent asthma.

The analysis included 45 patients with persistent asthma receiving low/moderate doses of inhaled corticosteroid. They were randomized to 12 weeks of supplementary treatment with salmeterol, 50 μ g bid; additional inhaled corticosteroid, fluticasone 100 μ g bid; or placebo. The effects of treatment on neutrophil numbers and levels of IL-8 and MPO in bronchoalveolar lavage (BAL) fluid were analyzed.

Initial BAL showed significant elevation of IL-8 in patients with persistent asthma compared with controls, though no difference in neutrophil numbers or MPO level. For the asthma patients, MPO was strongly correlated with IL-8 but only weakly correlated with neutrophil numbers in BAL fluid. Patients receiving the increased dose of inhaled corticosteroid had a significant increase in neutrophil numbers, while MPO and IL-8 levels were unaffected. By comparison, those receiving supplementary salmeterol showed reductions in IL-8 and MPO but no change in neutrophil numbers.

In patients with persistent asthma, giving supplementary salmeterol or increasing the inhaled corticosteroid dose yields contrasting effects on neutrophil numbers and MPO in BAL fluid. There is also a strong trend toward divergent effects on IL-8 levels. High IL-8 levels may play a significant pathogenetic role in asthma, even in patients receiving moderate doses of inhaled corticosteroids. In patients with stable asthma, the main function of IL-8 may be as a neutrophil activator.

COMMENT: It is generally accepted that β_2 -adrenergic agonists have little or no anti-inflammatory activity in vivo. However, studies of this issue have been largely confined to examining cytokine and inflammatory markers from eosinophils and mast cells. There is growing interest in the role of the neutrophil in the pathophysiology of asthma in certain patient populations. In vitro studies suggest that the β_2 -adrenergic agonists can have neutrophil-stabilizing properties. These investigators wished to determine the effects of adding salmeterol to low/moderate doses of fluticasone for 12 weeks, compared to increasing fluticasone dose, on BAL IL-18, neutrophil, and MPO levels. Salmeterol and fluticasone had opposite effects on IL-8, MPO levels, and neutrophil numbers. The combination was most effective in reducing IL-8 and MPO while stabilizing neutrophil numbers. The long-term clinical value of these findings remains to be determined, since the neutrophil is still not considered a major player in the asthma of most patients.

G. D. M.

Reid DW, Ward C, Wang N, et al: Possible anti-inflammatory effect of salmeterol against interleukin-8 and neutrophil activation in asthma in vivo.

Eur Respir J 21:994-999, 2003. ◆◆

Montelukast Add-on Therapy Improves Inflammatory Markers But Not Lung Function

IT has been suggested that add-on therapy with a leukotriene receptor antagonist (LTRA) might provide more complete suppression of airway inflammation in asthma patients taking inhaled corticosteroids. A previous study found no clinical benefit of add-on therapy with montelukast 10 mg in patients with moderate to severe asthma, but provided no information on surrogate markers of inflammation. Surrogate inflammatory markers and lung function measures were assessed in a randomized trial of montelukast add-on therapy for asthma.

The study included 22 patients with mild to moderate, persistent asthma receiving inhaled corticosteroids. All patients completed a 2-week run-in period using fluticasone propionate 250 μ g/salmeterol 50 μ g, 1 puff twice daily. In randomized, crossover fashion they then received 3 weeks of additional treatment with montelukast, 10 mg/d, and placebo. Patients continued on the fluticasone/salmeterol combination for the first 2 weeks, then switched to fluticasone only for the third week. The treatments were compared for their effects on pulmonary function and inflammatory markers.

Montelukast add-on therapy improved the provocative concentration of adenosine monophosphate required to cause a 20% reduction in FEV₁ by 1.4 geometric mean fold, compared with values at the end of the run-in period. Montelukast improved other surrogate inflammatory markers as well, including a 10-minute reduction in recovery time after bronchial challenge, a 2.1 ppb reduction in exhaled nitric oxide, and an 88 x 10⁶/L reduction in blood eosinophils. However, the ►►

addition of montelukast did not improve lung function or asthma symptoms. The fluticasone/salmeterol combination yielded better lung function than fluticasone plus montelukast.

Adding montelukast to fluticasone/salmeterol further improves surrogate inflammatory markers in patient with mild to moderate persistent asthma. However, montelukast does not yield further improvements in lung function, demonstrating the disconnection between the inflammatory process and lung function. Assessing lung function changes alone may fail to demonstrate the anti-inflammatory effects and long-term clinical benefits of LTRA therapy.

COMMENT: *The magnitude and clinical applicability of anti-inflammatory effects of the LTRAs have been vigorously debated. Some claim no effects at all, others claim no relevant clinical effects, while still others suggest a clinical impact with long-term use of a moderately anti-inflammatory agent that is easy to take and promotes adherence. This study examined the effects of short-term (3 weeks) montelukast added to salmeterol/high-dose fluticasone and fluticasone alone on objective lung function and surrogate inflammatory markers. There was significant improvement in surrogate inflammatory marker expression but not in objective lung function. Thus this small study continues the debate and further calls for long-term studies to determine the real clinical benefit (if any) of the anti-inflammatory properties of LTRAs.*

G. D. M.

Currie GP, Lee DKC, Haggart K, et al: Effects of montelukast on surrogate inflammatory markers in corticosteroid-treated patients with asthma.

Am J Respir Crit Care Med 167:1232-1238, 2003.

Survey Finds Low Rate of Needlestick Injuries in Allergy Practice

NEW Occupational Safety and Health Administration standards mandated by the 2001 Needlestick Safety and Prevention Act specify the use of "safer medical devices," where feasible, to help prevent accidental needlestick (ANS) injuries. This standard has been added to the California labor code and is under consideration elsewhere. The risk of pathogen transmission related to needlestick injuries in clinical allergy settings is unknown. California allergy practices were surveyed to assess the incidence of ANS injuries and resulting disease transmission.

A survey regarding ANS injuries was sent to 400 allergy practices, representing most such practices in California. Responses were received from 121 practices. Over a 2-year period, the responding practices used a total of 7.026 million 26-/27-gauge needles, two-thirds of them for subcutaneous allergy injections therapy. The overall incidence of ANS injuries was 45. This represented a rate of 6.41 ANS injuries per million, about 2% of the 267 per million rate reported in general medical settings. None of the ANS injuries in allergy offices led to disease transmission.

Three practices shared their experience with the use of safety needles. These nonscientific data suggested that using such devices actually increased the risk of ANS injury.

The rate of ANS injuries in allergy practice appears much lower than in other medical settings. No cases of disease transmission have been reported so far. The results question the cost implications and true benefits of switching to "safer medical devices" to prevent needlestick injuries.

COMMENT: *There is no question that full implementation of the Needlestick Safety and Prevention Act will result in procedural change and increased costs in most physicians' offices, especially allergists/immunologists. This study shows a much lower risk from needlestick injury in allergy practices compared with published hospital data, the primary source of information motivating the legislation. Nevertheless, we should strive to reduce the risk as much as possible, recognizing that there is a diminishing return for the increased cost when the risk of injury is minimal. Drawing the line for minimal acceptable risk is difficult, if not impossible.*

D. K. L.

Kanter LJ, Siegel C: Needle sticks and adverse outcomes in office-based allergy practices.

Ann Allergy Asthma Immunol 90:389-392, 2003. ♦♦

Evidence of Tolerance to β -Agonists Is Increased During Bronchoconstriction

PATIENTS who use β -agonists over a prolonged period develop evidence of tolerance to the bronchodilator effects of these drugs. Recent studies have suggested that such tolerance is particularly apparent during episodes of bronchoconstriction. The effects of severity of bronchoconstriction on tolerance to the acute bronchodilator effects of β -agonist drugs were studied.

The randomized, crossover trial included 15 adult patients with mild to moderate asthma. After a 2-week run-in period with no inhaled β -agonists, the patients received 4 weeks of treatment with salbutamol 400 μ g qid or placebo via Diskhaler. After the initial treatment period and a 2-week washout period, they were crossed over to the other treatment. On 3 days during each treatment period, patients underwent induced bronchoconstriction to mimic acute asthma attacks, reducing FEV₁ by 0%, 15%, and 30%. Immediately afterward, bronchodilator responses to salbutamol were assessed.

When studied after 4 weeks of taking salbutamol, patients showed a reduction in the acute response to β -agonist. The degree of attenuation was greater at greater levels of bronchoconstriction: FEV₁ area under the curve from 0 to 40 minutes was 11.2% at a 0% reduction in FEV₁, -14.6% at a 15% reduction, and -35.7% after a 30% reduction, compared with placebo.

For patients with asthma, regular use of an inhaled β -agonist is associated with a reduction in the acute bronchodilator response to the same drug, an effect that becomes more prominent at more severe levels of bronchoconstriction. For patients with severe asthma seen in

the emergency department, this may translate into clinical resistance to β -agonist therapy. Baseline FEV₁ measurements may also be lower for patients taking regular salbutamol, perhaps reflecting "rebound" bronchoconstriction caused by downregulation of β_2 -receptors in the airway. Although attenuation of the acute bronchodilator effect of β -agonists increases in linear fashion with degree of bronchoconstriction, this finding is highly variable among patients.

COMMENT: *It is well appreciated that chronic exposure to bronchodilators will ultimately induce tolerance. Indeed, studies have demonstrated adverse morbidity and mortality statistics as well. However, many individuals who abuse short-acting bronchodilators report no discernible decrease in efficacy. This study demonstrated that chronic use of salbutamol progressively reduced its bronchodilatory effect on methacholine-induced bronchoconstriction. The attenuated response was more evident with increasing doses of methacholine that produced greater bronchoconstriction. Such data support the concern that the adverse impact on tolerance to β_2 -agonists may be the most apparent when the effect is indeed the most.*

G. D. M.

Wraight JM, Hancox RJ, Herbison GP, et al: Bronchodilator tolerance: the impact of increasing bronchoconstriction.

Eur Respir J 21:810-815, 2003. ◆◆

REVIEWS OF NOTE

COMMENT: *The Tucson group continues to follow 78% of the 1,246 patients they studied at birth in 1980. This report summarizes their data to date. It is a "must-read" for all who care for children with asthma.*

S. M. F.

Taussig LM, Wright AL, Holberg CJ, et al: Tucson Children's Respiratory Study: 1980 to present.

J Allergy Clin Immunol 2003; 111:661-675.

COMMENT: *This is an excellent concise review of sarcoidosis, including the latest information related to genetic polymorphisms associated with increased risk of disease. Some of the newer therapeutic approaches are explored, including drugs that effectively suppress*

tumor necrosis factor- α in the setting of chronic disease.

E. J. B.

Baughman RP, Lower EE, du Bois RM: Sarcoidosis. Lancet 361:1111-1118, 2003.

COMMENT: *An excellent overview of chronic sinusitis, with emphasis on a detailed discussion of pathogenesis and treatment, including some of the newer surgical approaches.*

E. J. B.

Bachert C, Hörmann K, Mösges R, et al: An update on the diagnosis and treatment of sinusitis and nasal polyposis. Allergy 58:176-191, 2003.

COMMENT: *Many of us take for granted that a fixed proportion of our population suffers from allergic disease. However, defining "the lesion" that dictates why one person develops pathologic IgE responses and another does not is an imposing task. This excellent basic science review focuses on mechanisms of immunologic tolerance and how these processes may influence the development of allergic disease.*

S. A. T.

Akbari O, Stock P, DeKruyff RH, Umetsu DT: Mucosal tolerance and immunity: regulating the development of allergic disease and asthma.

Int Arch Allergy Immunol 130:108-118, 2003.

COMMENT: *The biological alterations that occur in the elderly have a significant effect on the regulatory immune cells governing the expression of asthma. These changes may induce specific airway hyperresponsiveness and also may reduce response to antiasthmatic drugs. This review focuses on such age-related changes, which tend to impede diagnosis and hinder the achievement of optimal therapy.*

E. J. B.

Vignola AM, Scichilone N, Bousquet J, et al: Aging and asthma: pathophysiological mechanisms.

Allergy 58:165-175, 2003.

COMMENT: *In the immunology of allergic disease, interleukin-13 has become recognized for its important proinflammatory effector functions. It probably plays a key role in the pathogenesis of asthma. It begins an intracellular signaling pathway that includes JAKS and STATS, which can be inhibited by SOCS and PIAS. Understanding these pathways may lead to an opportunity for new therapeutic targets in asthma.*

R. J. M.

Hershey GKK: IL-13 receptors and signaling pathways: an evolving web.

J Allergy Clin Immunol 111:677-690, 2003.

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