AllergyWatch®

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

A Publication of The American College of Allergy, Asthma & Immunology

Volume 6, Number 1 January-February 2004

Study Finds Current Asthma in 27% of Young New Zealanders

THE underlying reasons for the rising prevalence of asthma are unclear. Studies of clinic-based or high-risk samples do not necessarily indicate asthma outcomes in the general population. Data from a longitudinal, population-based study were used to assess asthma outcomes from childhood through young adulthood.

The analysis was based on a birth cohort of 1,139 children born in Dunedin, New Zealand, during 1972-73. Of these, 613 had complete follow-up data from age 9 through 26 years, including a symptom questionnaire, skin-prick testing, pulmonary function testing, and methacholine challenge studies.

By adulthood, wheezing was reported on at least one occasion by 72.6% of subjects and at least twice by 51.4%. The rate of asthma persisting or relapsing from childhood to young adulthood was 26.9%. Another 21.2% of subjects had transient wheezing, occurring only once, including 4.6% who reported wheezing only at age 26.

Persistent wheezing was predicted by house dust mite sensitization, odds ratio (OR) 2.41; and airway hyperresponsiveness, OR 3.00. Odds ratios for relapsed wheezing were 2.18 and 3.03, respectively. Other predictors of persistent wheezing were female sex, OR 1.71; smoking at age 21, OR 1.84; and younger age at the first episode of wheezing, OR 0.89 per year increase in age at onset.

In this population-based study, wheezing occurred at least once in nearly three-fourths of subjects from childhood to early adulthood and at least twice in more than half. The findings suggest a 27% rate of current asthma in young adults. Persistent or relapsed asthma is more likely to occur in subjects with early age at onset of wheezing. Impaired lung function appears to track from childhood into adulthood, and to be present already by age 9.

COMMENT: *I have often read that the prevalence of asthma is about 5% in the Western world, a number derived from cross-sectional analysis. This* longitudinal *study of unselected New Zealand children born in* ➤➤

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

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

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

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1972-73 and followed up through age 26 yields a cumulative incidence of 73% for wheezing at least once. The incidence of current asthma at age 26 years was 27%. House dust mite allergy, female sex, and smoking increased the odds of adult asthma. Most disturbing was the finding that a measurable degree of airway obstruction was already fixed by age 9 years in the persistent asthma group. In an accompanying editorial, Dr. Fernando Martinez surmises that the fast-growing airways of preschool children may be uniquely susceptible to the adverse consequences of chronic inflammation, consistent with the observation that allergies in young children predict more severe and persistent asthma. Now we need to find out how to contravene allergies in the youngest children!
R. J. M.
Sears MR, Greene JM, Willan AR, et al: A longitudinal, population-based cohort study of childhood asthma followed to adulthood.
N Engl J Med. 2003;349:1414-1422. ♦♦

Nonatopic Patients With Idiopathic Rhinitis May Be "Entopic" Instead

ALLERGIC rhinitis is associated with IgE-mediated allergic responses via a Th2 pathway. However, previous studies have shown allergen-specific IgE in the nasal secretions of some patients with rhinitis, despite the absence of atopy. This study sought evidence of an allergic, Th2 disease pathway localized to the nasal mucosa in nonatopic patients with rhinitis.

The study included two groups of patients with persistent rhinitis: 10 with nonatopic, idiopathic rhinitis and 11 with perennial allergic rhinitis. Twelve healthy controls were studied for comparison. All patients were tested for atopy by skin-prick testing and serum IgE measurement. In addition, nasal mucosa specimens were analyzed for specific IgE antibodies to dust mite and grass pollen, with biotin-labeled allergen used to localize specific allergen-binding antibodies.

Of the 11 patients with allergic rhinitis, 6 had specific antibodies for house dust mite allergen and 7 for grass pollen allergen in their nasal mucosa. None of the 10 patients with idiopathic rhinitis had specific antibodies for dust mite. However, 3 had specific antibodies for grass pollen, despite negative skin prick tests or serum IgE to this allergen. Neither type of antibody was detected in the mucosa of normal controls. The mucosal allergen co-localized to 10% of mast cells in the idiopathic rhinitis group, compared with 20% in the allergic rhinitis group.

This study demonstrates an allergic process localized to the nasal mucosa in some apparently nonatopic patients with idiopathic rhinitis. The authors propose the term "entopy" for this group of patients with mucosal allergic disease but negative results on skin-prick testing and serum IgE measurement. The study is the first to report mucosal allergen capture in this group of "nonallergic" patients.

COMMENT: *We have all evaluated patients who describe seasonal rhinitis symptoms but have negative skin tests. Using a technique that measures specific allergen binding to IgE in nasal biopsy specimens, these authors identified grass pollen binding in 3 of 10 nonatopic subjects with Th2-type nasal inflammation. They propose the term "entopy" to describe such patients. While it is premature to reclassify a third of our NARES patients as "entopics," these results certainly add to our understanding of localized allergic responses.*
S. A. T.
Powe DG, Jagger C, Kleinjan A, et al: "Entopy: *localized mucosal allergic disease in the absence of systemic responses for atopy.*
Clin Exp Allergy. 2003;33:1374-1379. ♦♦

GM-CSF Polymorphisms Linked to AD Risk in Children

THE genes involved in inheritance of atopic dermatitis (AD) are unknown. In the skin, the Langerhans' cell acts as the antigen-presenting dendritic cell responsible for triggering immune responses. Genetic predisposition to AD may therefore be affected by factors acting on Langerhans' cell. Polymorphisms affecting factors involved in the function of the Langerhans' cells of the skin were analyzed for their association with the presence and severity of AD.

The study included 113 children with AD seen at a British referral center, as well as 114 non-AD controls. Known functional polymorphisms of interleukin-1β and tumor necrosis factor-α were analyzed for their relationship to AD. Also assessed were newly discovered polymorphisms in the promoter region of the granulocyte/macrophage colony stimulating factor (GM-CSF) gene.

The frequency of both the -677 and -1916 polymorphisms of the GM-CSF gene differed significantly between AD and control children. The findings suggested two common GM-CSF haplotypes: -677*C -1916*C and -677*A -1916*T. Children who did not have a C allele were at increased risk of AD, with odds ratios of 2.3 for the -677 polymorphism and 1.9 for the -1916 polymorphism. None of the children in the most severe AD group (based on percent of body surface area involved) had the C/C GM-CSF genotype, compared with 16% of the control group. In contrast, the A/A genotype was present in 50% of children with severe AD vs 16% of controls.

These two GM-CSF promoter polymorphisms appear to influence the presence and severity of AD in children. The exact functions of the polymorphisms remain unknown. However, the results suggest that factors affecting dendritic cell maturation influence the genetic predisposition to develop AD.

COMMENT: *Atopic dermatitis is certainly an inheritable disease--perhaps more clearly so than other atopic diseases--but its genetic basis is unknown. These authors speculated that gene affecting dendritic cells, which are at the front end of immunologic reactivity, might be related to development and inheritance of AD. By studying polymorphisms of the gene that codes for GM-CSF, which promotes development and migration of dendritic cells, they found this gene to be highly associated with susceptibility to AD. This suggests that, in addition to focusing on medications aimed at mediators, we might someday have better success upstream, at the dendritic cell or antigen presentation level.*
R. J. M.

Rafatpanah J, Bennett E, Pravica V, et al: Association between novel GM-CSF gene polymorphisms and the frequency and severity of atopic dermatitis.
J Allergy Clin Immunol. 2003;112:593-598. ♦♦

Study Questions Cross-Reactivity Between Sulfonamide Antibiotics and Nonantibiotics

ALLERGIC reactions to sulfonamide antibiotics are a frequent occurrence. Many widely used drugs are sulfonamides, but not antibiotics. It is unclear whether it is safe to give these sulfonamide nonantibiotics to patients with previous allergic reactions to sulfonamide antibiotics.

The U.K. General Practice Research Database was used to identify 969 patients (study group) who had a history of allergic reaction to a sulfonamide antibiotic and who received a sulfonamide nonantibiotic at least 60 days later. The rate of allergic reactions to the second drug was 9.9%, compared with 1.6% for a group of 19,257 patients with no history of reaction to a sulfonamide antibiotic. The adjusted odds ratio for reaction to a sulfonamide nonantibiotic in the study group was 2.8 (95% confidence interval 2.5 to 3.1).

However, for patients with a history of reaction to a sulfonamide antibiotic, the risk of subsequent reactions was even greater after receiving a penicillin, adjusted odds ratio 3.9 (3.5 to 4.3). In the study group, the risk of reaction to a subsequent sulfonamide nonantibiotic was lower than the risk of a reaction to a subsequent penicillin, adjusted odds ratio 0.7 (0.5 to 0.9).

Patients with allergic reaction to a sulfonamide antibiotic are at risk of subsequent reaction to a sulfonamide nonantibiotic. However, this risk appears to reflect a general tendency to drug allergies, rather than any cross-reaction among different sulfonamide drugs. A history of allergic reactions to sulfonamides or penicillins may be considered a risk factor for reactions to other drugs, rather than a specific contraindication to sulfonamides.

COMMENT: *There are many "sulfa drugs" that are not antibiotics. Examples include thiazide diuretics, some oral hypoglycemic agents, and probenecid. This study showed that, as expected, the risk of an allergy to a sulfa non-antibiotic was increased in patients who were allergic to a sulfa antibiotic. But the risk was* was not as great *as in those who received penicillin, a chemically unrelated class of drug. Thus it may be inferred that one drug allergy of any kind confers an increased risk of other drug allergies, irrespective of chemical class, and that sulfa non-antibiotics can be prescribed to patients with sulfa antibiotic allergy with reasonable safety.*
R. J. M.

Strom BL, Schinnar R, Apter AJ, et al: Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics.
N Engl J Med. 2003;349:1628-1635. ♦♦

In Nut Allergy, Test Results Don't Predict Clinical Severity

ACCURATE diagnosis is essential in patients with peanut and nut allergy. However, not all patients who are sensitized to nuts--ie, have specific IgE--experience allergic reactions. The relationship between test results and clinical manifestations was evaluated in 1,000 patients with peanut or nut allergy, including correlation between the results of skin-prick testing (SPT) and CAP testing.

All patients had a typical history of allergic reaction to one or more peanut or tree nuts, or tolerance to up to five nuts, and underwent SPT and/or CAP testing. The test results were compared with the severity-graded reactions. Across all five nuts, the severity of reactions was unrelated to the diameter response on SPT. This lack of correlation held on examination of peanut alone; only Brazil nut showed a significant association between increasing SPT diameter and severity of reactions.

Over 90% of patients had an SPT result of greater than 4 mm to the nut causing their index reaction. However, when tested for the nut causing the most severe reaction, only 22% had a positive SPT result, with 30% having a CAP result of 15 kU/L or greater. Of patients tolerating a specific nut, 43% had an SPT reaction of 3 to 7 mm while 3% had reactions of 8 mm or greater. On CAP testing, 35% of tolerant patients had a positive result, including 5% with results of 15 kU/L or greater. The concordance rate between SPT and CAP was 66%.

For patients with peanut or nut allergy, the severity of reaction cannot be predicted from the magnitude of reaction on SPT or CAP. Although SPT is more reliable in confirming the presence of allergy, clinical severity is still unpredictable for patients in the "gray area" between 3 and 7 mm. On CAP testing, the results are "falsely reassuring" in 22% of cases and misleading in 40% of positive tests. The history is critical to assessing the severity of peanut or nut allergy. However, nut tolerance is rare when the SPT reaction is 8 mm or larger or the CAP result is 15 kU/L or greater.

COMMENT: *Despite recent advances in food allergy diagnostics, the practicing clinician is often faced with discordant history and testing results. This 1,000-patient observational study highlights the limitations of currently available tests for peanut and tree-nut allergy. For example, among patients with a high pretest probability of nut allergy and a positive SPT to the nut in question, the immuno-CAP result was negative 22% of the time. In addition, for peanuts and all other nuts except Brazil nut, the clinical severity of allergy did not correlate with the magnitude of either the SPT or immuno-CAP results. The accompanying editorial discusses the results in context of results from smaller studies employing blinded oral food challenges. These results point to the need for additional improvements in our ability to diagnose and stratify risk in this increasingly prevalent disease.*
S. A. T.
Clark AT, Ewan PT: Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance.
Clin Exp Allergy. 2003;33:1041-1045. ♦♦

GERD, But Not Steroid Dose, Predicts More Severe Asthma

IT is important to identify factors associated with greater asthma severity among patients receiving specialty care. Patients attending an asthma referral center were analyzed to assess factors associated with more severe asthma, including the use of adequate doses of inhaled corticosteroids.

The retrospective study included 149 patients seen at the specialty clinic over a 2.5-year period. On assessment of 14 potential causative or contributive factors, patients with mild asthma had a mean of 2.9 factors compared to 3.5 in those with moderate to severe asthma. Factors independently associated with more severe asthma included older age, male sex, symptomatic gastroesophageal reflux disease (GERD), and chronic sinusitis. Sensitization and exposure to common allergens were not significant factors.

The use of inhaled steroid doses meeting National Heart, Lung, and Blood Institute guidelines was assessed. Most patients received suboptimal inhaled steroid therapy--about 70% in both the mild and moderate-to-severe asthma groups. Patients with mild persistent asthma were more likely to receive suboptimal doses of inhaled steroids.

Certain factors are related to more severe asthma among patients in a referral clinic, especially GERD and sinusitis. Most patients in this population are not receiving adequate doses of inhaled corticosteroid therapy, with no difference between asthma severity groups.

COMMENT: *This retrospective study included only patients seen at a university-based asthma clinic. The results point to an underutilization of inhaled corticosteroids that is independent of asthma severity. This was somewhat surprising to the authors, as they had hypothesized that underutilization of inhaled corticosteroids would be a greater problem among patient with more severe asthma. In keeping with earlier studies, symptomatic GERD and sinusitis appear to be prominent markers of increasing asthma severity.*
S. A. T.
Liou A, Grubb JR, Schechtman KB, Hamilos DL: Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care.
Chest. 2003;124:1781-1788. ♦♦

Findings in CRS Patients Reaffirm the "Allergic March"

MORE than half of patients with chronic rhinosinusitis (CRS) have asthma as well. Both diseases are associated with eosinophilic inflammation, but the presence of epithelial damage and basement membrane thickening in CRS is unclear. These histopathologic changes were assessed in specimens of sinonasal mucosa from surgical patients with CRS.

The analysis included histologic specimens from a random sample of 22 patients who underwent ➤➤

endoscopic sinus surgery for refractory CRS. Independent observers assessed the tissues for evidence of eosinophilic inflammation, epithelial damage, and basement membrane thickening. Tissues from 4 healthy controls were studied for comparison.

Epithelial damage was noted in all CRS patients, with 91% showing stage 3 erosion of the sinonasal epithelium down to the basement membrane. Ninety-five percent of CRS patients had stage 2 basement membrane thickening. All samples from CRS patients included areas of abundant eosinophilia, with other areas showing no eosinophils. This heterogeneous pattern of eosinophilic inflammation was similar in patients with and without allergy, but was not seen in the control subjects.

Like patients with asthma, CRS patients show histologic evidence of heterogeneous eosinophilic inflammation and airway remodeling. The findings add to the evidence that the sinonasal disease process in CRS is the same as the lower-airway disease process in asthma. The erosion and epithelial damage observed in these patients could account for the frequent bacterial exacerbations occurring in CRS.

COMMENT: *These Mayo Clinic researchers found thickening of the basement membrane and eosinophilic inflammation in biopsy specimens from both the nose and lungs of 22 patients having surgery for CRS. Twenty of the patients had diagnosed asthma or methacholine sensitivity, but only 45% were considered allergic. The fact that similar findings were noted in the nose and lungs gives further credence to the concept of the united airway and suggests a single pathophysiologic process involving both end organs.*
S. M. F.

Ponikau JU, Sherris DA, Kephart GM, et al: Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma?
J Allergy Clin Immunol. 2003;112:877-882. ♦♦

To Prevent Wheezing, Breast Is Best

BREAST-fed infants are at reduced risk of wheezing, although the breast-milk components responsible for this protective effect are unknown. Recent studies have demonstrated the presence of cytokines, including transforming growth factor-β (TGF-β), in human breast milk. The relationship between the TGF-β content of breast milk and the occurrence of wheezing in infancy was assessed.

The prospective analysis included 243 mothers and infants in Tucson, Ariz., enrolled in the Infant Immune Study. All had complete information on breast-feeding and infant wheezing through the first year of life. The breast-feeding rate was high, with 48% of infants receiving breast milk for at least 6 months. When the infants were a mean of 11 days old, a breast milk sample was obtained for enzyme-linked immunosorbent assay measurement of TGF-β and other cytokines.

Forty percent of the infants had at least one episode of wheezing; 15 of these 90 infants had frequent wheezing episodes. There was an inverse, linear association between the TGF-β dose received in breast milk and the infants' risk of wheezing, but not for any other cytokine measured. The reduction in risk of any wheezing was significant only for infants with a long duration of breast-feeding and a medium-high TGF-β concentration: odds ratio 0.22, compared with short-duration/low TGF-β infants.

The protective effect of breast-feeding against wheezing in infancy may be related to the presence of TGF-β in breast milk. The mechanism of protection may involve prevention of sensitization or effects on infant lung development. The study is one of the first to look at the effects of breast-milk cytokines on infant health.

COMMENT: *Using data from the prospective Infant Immune Study, these researchers found a significant relationship between the dose of TGF-β from nursing mothers and a protective effect against wheezing illness in their children by 1 year of age. The fact that 63% of the 243 children studied were breast-fed for at least 3 months and 48% for at least 6 months enables a large-enough sample for analysis. A major limitation of this study is that only one sample of breast milk was obtained about 2 weeks postpartum, although the wheezing illnesses were evaluated at 1 year. There may be variation in cytokine production in human milk over time. In spite of this, the new data are convincing and add to the argument that "Breast is best."*
S. M. F.

Oddy WH, Halonen M, Martinez FD, et al: TGF-β in human milk is associated with wheeze in infancy.
J Allergy Clin Immunol. 2003;112:723-728. ♦♦

Feline Exposure Forestalls Asthma Disposure

CHILDREN who grow up in farm environments appear to be at reduced risk of atopic disease. However, the impact of early exposure to pets remains uncertain. The effects of type, time, and intensity of pet exposure on risk of childhood asthma and hay fever were assessed.

The cross-sectional survey study included data on 8,216 children, aged 5 to 7 years, living in rural areas of Germany but not on farms. International Study of Asthma and Allergies in Childhood criteria were used to define the presence of asthma and hay fever; wheezing and asthma were considered atopic if the affected child had hay fever or atopic dermatitis as well. The relationship between atopic disease and pet exposure--currently and during the first year of life--was assessed.

Children exposed to furred pets in the first year of life only had a significantly increased prevalence of hay fever symptoms, while those with continuous pet exposure were at lower risk of atopic asthma. These relationships were little changed on analysis stratified by family history of atopic disease.

However, when stratified by type of animal, significant associations were noted only for cat exposure. Children exposed to cats from the first year of life onward were at reduced risk of atopic asthma, if ➤➤

the cats were allowed in the child's bedroom. None of 296 children with this history developed atopic asthma. They were also at low risk of atopic wheezing during the past year.

Children with intensive early exposure to cats appear to be protected against childhood asthma. Allowing cats in the child's bedroom during the first year of life may be a relevant marker of this degree of exposure. No protective effect is noted for current intensive exposure to cats.

COMMENT: *This large study finds no convincing association between asthma and allergic rhinitis and pet exposure. The investigators do find that children who are intensively exposed to cats during the first year of life have a significantly reduced risk of asthma, compared to counterparts with no furred pets. There are some definite limitations in this study, but the data are striking. How did we overlook this for so many years?*
E. J. B.

Oberle D, von Mutius E, von Kries R: Childhood asthma and continuous exposure to cats since the first year of life with cats allowed in the child's bedroom.
Allergy. 2003;58:1033-1036. ♦♦

An Unexpected Benefit of Inhaled Steroids

SEVERAL factors may lead to an increased risk of cardiovascular disease among patients with asthma. By reducing asthma exacerbations and improving disease control, inhaled corticosteroids may act to lower this cardiovascular risk. The effects of inhaled corticosteroid use on myocardial infarction risk were examined in a large, population-based cohort.

Saskatchewan provincial heath insurance data were used to identify a cohort of 30,569 patients, aged 5 to 44 years, who received at least three prescriptions for antiasthma drugs between 1975 and 1991. With follow-up to 1997, age 55 years, or death, 105 patients had myocardial infarction. These cases were matched for time, age, and sex to 933 controls.

For patients receiving inhaled corticosteroids in previous year, the adjusted rate ratio for myocardial infarction was 0.56 (95% confidence interval 0.32 to 0.99), compared with nonusers. For each canister of steroid used during this time, myocardial infarction risk decreased by 12%. The protective effect of inhaled corticosteroid use was most pronounced for patients with markers of asthma severity: rate ratio 0.19 (0.04 to 0.97), compared with 0.78 (0.41 to 1.51) for those with no such markers.

For patients with asthma--especially more severe asthma--inhaled corticosteroid therapy may reduce the risk of myocardial infarction. The extent of risk reduction is about 50%, after adjustment for other asthma treatments, disease severity, and myocardial infarction risk factors. Further studies are needed, especially in older patients.

COMMENT: *These well-known investigators made use of the Saskatchewan Health databases to create a large population-based cohort of patients aged 5 to 44 years using antiasthma drugs between 1975 and 1991. Remarkably, the results showed that inhaled corticosteroid use was associated with a decrease in the risk of myocardial infarction. In reviewing risk/benefit potentials with patients about to start on this therapy, it appears that we can add a definite positive factor on the benefit side of the ledger!*
E. J. B.

Suissa S, Assimes T, Brassard P, Ernst P: Inhaled corticosteroid use in asthma and the prevention of myocardial infarction.
Am J Med. 2003;115:377-381. ♦♦

Data Show Very Low Risk of Vaccine-Related Anaphylaxis

VACCINE-related anaphylactic reactions have been reported. The risk of such reactions is unknown, but appears small. A combined HMO data base was used to assess the rate of anaphylaxis occurring after vaccinations in children.

The Vaccine Safety Datalink study included data on a total 7,644,049 doses of vaccine given to pediatric patients at four HMOs in California, Oregon, and Washington. Medical records were searched for cases of anaphylactic shock or other adverse reactions from the vaccines. The search was limited to reactions occurring within 2 days after vaccination.

Five cases of possible vaccine-related anaphylaxis were identified, for a risk of 0.65 reactions per 1 million doses of vaccine. None of the reactions was fatal. Most patients received a combination of vaccines before the event, including measles-mumps-rubella, hepatitis B, diphtheria-tetanus, diphtheria-tetanus-pertussis, *Haemophilus influenzae* type b, and oral polio vaccine.

Data from one HMO were reviewed to assess other types of allergic reactions as well. There was 1 case in 653,990 vaccine doses, a rate of 1.53 reactions per 1 million doses.

This extensive data base suggests a very low rate of anaphylactic reactions to routine childhood vaccines. The exact component causing the reactions--vaccine antigen, animal protein, or antibiotics--is unknown. Clinicians must be prepared to manage anaphylactic reactions if they occur, and should avoid subsequent doses in patients who react to a vaccine.

COMMENT: *It is comforting to know that in the United States, the risk of a systemic allergic-like reaction following routine infant immunizations is very low. In this HMO population, more than 7.5 million doses of over 14 different types of vaccine were administered between 1991 and 1997. Only 4 infants had symptoms of reactions that were possibly related to the injection. (An additional 17-year-old also reacted.) This gives an overall risk rate between 0.65 to 1.53 per 1 million vaccine doses. Of the five cases, four occurred within 2 hours (one 48 hours later). Three patients required epinephrine (including the late reactor). Usually multiple vaccines were given at once; the exact cause of the reaction was not studied.*
J. A. A. ➤➤

Bohlke K, Davis RL, Marcy SM, et al: Risk of anaphylaxis after vaccination of children and adolescents. **Pediatrics.** 2003;112:815-820. ♦♦

β_2-Adrenergic Receptor Genotype Linked to Childhood Asthma Phenotype

PREVIOUS studies have linked polymorphisms of the β_2-adrenergic receptor (*B2AR*) gene to differing asthma phenotypes. However, the results of these analyses have been inconsistent across studies. Children from the Childhood Asthma Management Program (CAMP) and their families were studied to assess the relationship between specific *B2AR* gene polymorphisms and asthma phenotype.

The study included DNA samples from 707 CAMP participants, providing information on 650 sibships; and from the parents of enrolled children. Genotyping studies focused on eight single nucleotide polymorphisms (SNPs) of the *B2AR* gene. Associations between the SNPs and haplotypes were assessed by qualitative and quantitative phenotypic analyses.

The SNP -654 and SNP +46 genotypes were significantly related to postbronchodilator FEV_1. This association held whether postbronchodilator FEV_1 was expressed as a qualitative (ie, less than 80% of predicted) or quantitative phenotype. In addition, SNP +523 was significantly associated with response to bronchodilators, whether as a percentage of initial or predicted FEV_1.

Most of the haplotypic variation observed was limited to three common haplotypes. The haplotype analysis supported the relationship of *B2AR* variants with spirometric parameters and bronchodilator responsiveness.

Specific variants of the *B2AR* gene are related to indicators of clinical asthma phenotype in children with mild to moderate asthma. Variants in or near *B2AR* seem to have an impact on pulmonary function measures and responsiveness to bronchodilators, depending on the region of the gene affected. The conflicting results of previous studies may be explained by the existence of several different asthma-related genetic factors in this region.

COMMENT: *We continue to learn more from the CAMP study. Over 700 asthmatic children and their parents underwent genotyping to eight different SNPs in the* B2AR *gene. Significant associations were found at three: SNP -654 and SNP +46 with postbronchodilator FEV_1 and SNP +523 with bronchodilator responsiveness. One of the strengths of this study is the family-based analysis, which is less susceptible to population stratification than the usual case-control study designs. Although the significance of the* B2AR *gene is still unclear, the fact that variations in or near this gene are important for lung function or responsiveness to medications suggest that it will probably play an important role in the identification of asthmatics in the future.*
S. M. F.
Silverman EK, Kwiatkowski DJ, Sylvia JS, et al: Family-based association analysis of β_2-adrenergic receptor polymorphisms in the Childhood Asthma Management Program.
J Allergy Clin Immunol. 2003;112:870-876.

How Does Severe Asthma Differ in Children vs Adults?

PATIENTS with severe asthma account for much of the total morbidity and costs associated with this disease. More data are needed on the clinical characteristics of children and adults with severe asthma.

This issue was addressed in a retrospective study of 150 adults and 125 children (mean age 34.4 and 12.5 years, respectively) referred for evaluation of difficult-to-control asthma over a 4-year period. All patients underwent lung function testing, glucocorticoid pharmacokinetic studies, and lymphocyte stimulation assays.

The pediatric and adult patients were similar in terms of their need for high-dose inhaled steroids and long-term oral steroid therapy and previous history of intubation. However, mean FEV_1 was 74.0% predicted in children vs 57.1% predicted in adults. Mean airway resistance was 140.3% vs 311.0% predicted and mean total lung capacity 116.4% vs 105.3% predicted, respectively.

The children were more likely to be male and had greater in vitro responsiveness to glucocorticoids. Asthma duration was significantly related to severity of lung function impairment in children and in adults with childhood-onset asthma, but not in patients with adult-onset asthma. In the latter group, lung function was just as compromised as in adult patients with a longstanding asthma.

Among patients with difficult-to-control asthma, lung function is less impaired for pediatric patients than adults. These children may have a long history of symptoms and episodes of acute lung function decline before developing chronic airflow limitation.

COMMENT: *Severe asthma is a difficult disease process to treat, and our knowledge base remains limited. This study sought to identify characteristics of severe asthma in both children and adults. Data were collected from 275 patients with difficult-to-control asthma who were referred to National Jewish Center between 1997 and 2001. Children had less severe airflow limitation over time and greater in vitro responsiveness, although they required longer courses of oral corticosteroids to respond. Adults did not experience significant deterioration in lung function over time, although they often had persistently severe airflow obstruction. Again, the results emphasize the importance of identification and prevention for patients at risk for severe asthma.*
A. L. L.
Jenkins HA, Cherniak R, Szefler SJ, et al: A comparison of the clinical characteristics of children and adults with severe asthma.
Chest. 2003;124:1318-1324. ♦♦

Trial Compares Add-On Therapy with Montelukast vs Salmeterol

FOR asthma patients whose disease is inadequately controlled using inhaled corticosteroids alone, adding a long-acting β-agonist or leukotriene receptor antagonist reduces exacerbation rate and improves quality of life. However, few studies have compared these two approaches directly.

One thousand four hundred ninety adult asthma patients whose symptoms were uncontrolled by inhaled corticosteroids alone were randomized to receive add-on therapy with montelukast or salmeterol. All had had asthma for at least 1 year, with a baseline FEV_1 of 50% to 90% predicted and improvement of 12% or better with β-agonist treatment. Treatment with montelukast-fluticasone or salmeterol-fluticasone continued for 1 year.

The percentage of patients reaching the main outcome measure of at least one asthma exacerbation was 20.1% with montelukast-fluticasone and 19.1% with salmeterol-fluticasone. The salmeterol-fluticasone group had increased FEV_1 before β-agonist treatment and increased morning peak expiratory flow. The two treatments were similar in terms of FEV_1 after β-agonist use, asthma-specific quality of life, and nighttime awakenings. Patients receiving montelukast-fluticasone had greater reductions in peripheral blood eosinophil count.

For adults with continued asthma symptoms on inhaled fluticasone, add-on therapy with montelukast is at least as effective as salmeterol in controlling disease exacerbations. The industry-sponsored study concludes that adding a leukotriene receptor antagonist to an inhaled corticosteroid is a reasonable therapeutic option in this group of patients.

COMMENT: *Eight European centers enrolled a total of 1,490 patients in this year-long, double-blind trial comparing the addition of montelukast or salmeterol in asthmatics whose disease was not controlled with inhaled corticosteroids alone. Using the primary endpoint of asthma exacerbations, montelukast-fluticasone compared favorably to the salmeterol-fluticasone regimen. Other efficacy endpoints included change in FEV_1 (salmeterol-fluticasone was superior) and sputum and peripheral blood eosinophilia (montelukast-fluticasone was superior). Patient-assessed quality of life was similar between groups. The authors conclude that adding montelukast could provide equivalent clinical control compared with adding salmeterol. Current published guidelines disagree, but the real quandary is which endpoint is best when evaluating outcomes in our chronic asthma patients.*

S. M. F.

Bjermer L, Bisgaard H, Bousquet J, et al: Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. **BMJ.** 2003;327:891-896. ♦♦

Th1 Responses to Rhinovirus Linked to Asthma Severity

ASTHMA has been linked to increased production of interleukin (IL)-5 and other Th2 cytokines. However, some studies have reported deficiencies in production of Th1 cytokines such as interferon-γ (IFN-γ). Rhinovirus and other respiratory viruses are important triggers of asthma exacerbations. The Th1 and Th2 responses to rhinovirus were studied in peripheral blood mononuclear cells from asthma patients.

Cells were isolated and cultured from 19 adult patients with mild to moderate allergic asthma. The cells were then incubated for 6 days with rhinovirus-16. The IFN-γ and IL-5 responses were assessed by enzyme-linked immunosorbent assay, and the results compared with measures of airway responsiveness to methacholine and airway obstruction.

Incubation with rhinovirus-16 led to significantly increased production of IFN-γ, but not IL-5. The rhinovirus-induced increase in IFN-γ was correlated with the patients' methacholine PD_{20}. In addition, the ratio of rhinovirus-induced IFN-γ to IL-5 was correlated with FEV_1 percent predicted.

In contrast, the IL-5 response to rhinovirus was unrelated to any asthma severity marker. The IFN-γ response to rhinovirus varied between subjects but was reproducible within subjects.

The Th1 response to rhinovirus is significantly related to measures of asthma severity, while the Th2 response is not. These in vitro findings support the hypothesis that defective Th1 cytokine responses to viruses and allergens play an important role in asthma. Additional studies are needed to clarify the relationship between reduced Th1 responses and markers of asthma severity.

COMMENT: *The Th1/Th2 paradigm is accepted by most allergists as important in the inflammatory pathophysiology of asthma. Yet many would consider the imbalance to be an excess of Th2 cytokines (IL-4, IL-5, and IL-13), which has also been associated with allergic diseases such as rhinitis. However, an extremely common exacerbator of asthma is respiratory infections, particularly with rhinovirus. This study examined the Th1 (IFN-γ) and Th2 (IL-5) cytokine responses of peripheral blood mononuclear cells from allergic asthma patients incubated with a common rhinovirus. Results showed that decreased IFN-γ production was associated with asthma severity (methacholine PD_{20}). There was no association with IL-5 production. This indicates that asthma severity, at least in response to rhinovirus exposure, is related to a deficiency of Th1 (antiviral) responses rather than an excess of Th2 cytokines.*

G. D. M.

Brooks GD, Buchta KA, Swenson CA, et al: Rhinovirus-induced interferon-γ and airway responsiveness in asthma.
Am J Respir Crit Care Med. 2003;168:1091-1094.

Acute Stress Lowers Early Pulmonary Response to Allergen

PREVIOUS reports suggest that stress may lead to worsening of asthma. One study linked chronic stressful life events in patients with allergic asthma to increased airway inflammation 6 to 24 hours after antigen inhalation. This study looked at the effects of acute stress on the early pulmonary response to antigen in women with allergic asthma.

In random order, 8 women with allergic asthma were studied during an acute stress visit, in which they were to tell about an emotionally stressful event in their lives; and a control, nonstress visit. At each visit, the women underwent a series of challenges with increasing concentrations of inhaled allergen. Differences in blood pressure, heart rate, and FEV_1 were compared between visits.

Systolic and diastolic blood pressure and heart rate were significantly increased during the stress visit compared with the nonstress visit. In most patients, peak increases in blood pressure were measured at the end of the allergen-inhalation protocol.

However, in 6 of the 8 patients, the reduction in FEV_1 at the same last dose of allergen was significantly less on the stress visit: mean 11.2%, compared with 15.0% on the nonstress visit. Just 1 patient showed potentiation of the pulmonary response to allergen during the stress visit.

In contrast to the authors' hypothesis, acute stress seems to be associated with a reduced early pulmonary response to allergen in women with allergic asthma. The measured changes in cardiovascular parameters suggest enhanced sympathetic responsiveness, although the study did not include measurement of adrenaline levels. The authors note that their preliminary findings apply only to the effects of "verbally re-experiencing" emotional stress.

COMMENT: *There is increasing recognition by both patients and physicians of the adverse effects of stress on asthma. In most cases, the stress is more chronic than acute. Immune studies have suggested opposite immune effects of chronic and acute stress models in humans, with chronic stress showing Th2 predominance and acute stress showing a more Th1-dominant pattern. This small study looked at the effects of an acute laboratory speech stressor on allergen-induced decrease in FEV_1. The results showed an attenuation of the decrease in FEV_1 after acute stress, compared with a nonstress visit. This suggests a potential protective effect of acute stress, known to be mediated by catecholamines, on airway reactivity in allergic asthma.*
G. D. M.

Laube BL, Curbow BA, Fitzgerald ST, Spratt K: Early pulmonary response to allergen is attenuated during acute emotional stress in females with asthma.
Eur Respir J. 2003;22:613-616. ♦♦

Steroid Is Ineffective for Viral Wheeze

CHILDREN aged 1 to 5 years commonly experience episodes of wheezing during viral colds. Oral prednisolone has been recommended for children with "preschool viral wheeze," although there are conflicting data regarding the efficacy of this approach. This randomized trial evaluated the benefits of a short course of oral prednisolone for preschool-aged children with viral wheeze.

The study included 217 children, aged 1 to 5 years, admitted to a U.K. hospital with viral wheeze. The patients were stratified for high vs low systemic eosinophil priming. They were then randomized to receive oral prednisolone for their next episode of viral wheeze--20 mg once daily for 5 days, initiated by parents--or placebo. Outcomes analysis included 120 children with a subsequent episode of viral wheeze: 51 treated with prednisolone and 69 with placebo.

Seven-day daytime and nighttime respiratory symptom scores were not significantly different between the steroid and placebo groups. There was also no difference in the rate of hospitalization for subsequent episodes. The lack of difference between treatments held for both the high-primed and low-primed subgroups.

For young children with preschool viral wheeze, parent-initiated treatment with oral prednisolone does not appear beneficial. Even for children with high systemic eosinophil priming, a short course of oral steroid does not reduce the symptoms or hospitalization risk during subsequent episodes of viral wheeze.

COMMENT: *Young children aged 1 to 5 years frequently experience episodic wheezing during viral respiratory infections--ie, the wheezy bronchitis phenotype. There is a tendency to treat such episodes with a course of oral steroids. Evidence that this practice results in a beneficial outcome is lacking. This controlled study shows no benefit from a short course of oral corticosteroid for viral wheeze--even in patients with above-average eosinophil priming.*
E. J. B.

Oommen A, Lambert PC, Grigg J: Efficacy of a short-course of parent-initiation oral prednisolone for viral wheeze in children aged 1-5 years:randomised controlled trial.
Lancet. 2003;362:1433-1438. ♦♦

Maternal Smoking May Block Benefits of Placental Cytokines

THE antenatal environment may influence atopy and asthma risk. Prenatal cytokines are believed to play a key role in maturation of the fetal immune system. This study assessed relationships between cord blood levels of Th1/Th2 cytokines and later risk of asthma and atopy.

Enzyme-linked immunosorbent assays were used to measure cytokine levels in cryopreserved cord-blood serum samples from 407 children. The relation- ➤➤

ship between cord-blood cytokine levels and asthma and atopy outcomes at age 6 was assessed, including the role of family, antenatal, and perinatal factors.

Risk of physician-diagnosed asthma was significantly lower for children with detectable interleukin-4 and interferon-γ in their cord-blood samples, with adjusted odds ratios of 0.60 for both cytokines. These children also had lower rates of current asthma, odds ratio 0.59 for interleukin-4 and 0.39 for interferon-γ; and current wheeze, odds ratio 0.55 and 0.52, respectively. Rates of sensitization to certain inhalant allergens were lower as well.

Children with high cord-blood levels of tumor necrosis factor-α were at lower risk of atopy, although asthma rates were unaffected. Propensity-score adjustment, performed to assess the causal role of cytokines, had no major effect on the associations. Offspring of mothers who smoked during pregnancy had lower cord-blood levels of interleukin-4 and interferon-γ, odds ratios 0.65 and 0.58, respectively; and a higher rate of wheeze at age 6, odds ratio 1.85.

Fetal-placental production of cytokines--including interleukin-4, interferon-γ, and tumor necrosis factor-α--may affect the risk of childhood asthma and atopy. The effects of these Th1/Th2 cytokines appear independent of relevant antenatal and perinatal variables. Maternal smoking may adversely affect fetal-placental cytokine production.

COMMENT: *This interesting study shows that higher levels of cord blood interleukin-4 and interferon-γ are associated with a lower risk of asthma outcomes. As well, higher levels of tumor necrosis factor-α are associated with a lower risk of atopy. These authors also show a dose-response effect on cord-serum cytokine levels with maternal smoking, either before or during pregnancy. Although very interesting, these observations should be viewed with caution because of the many events and exposures occurring during birth.*
E. J. B.
Macaubas C, de Klerk NH, Holt BJ, et al: Association between antenatal cytokine production and the development of atopy and asthma at age 6 years.
Lancet. 2003;362:1192-1197. ♦♦

Aspirin-Sensitive Asthma Linked to Abnormal Regulation of 15-HETE

ASPIRIN-induced rhinosinusitis-asthma is a common problem, usually associated with severe asthma and the need for chronic systemic steroids. The mechanism is unknown but may involve alterations in arachidonic acid metabolism. A recent study showed enhanced production of 15-hydroxyeicosatetraenoic acid (15-HETE) in nasal polyp endothelial cells from aspirin-sensitive patients.

Enzyme immunoassays were used to study production of 15-HETE and other eicanosoids by peripheral blood leukocytes (PBLs) from two 24 aspirin-sensitive and 18 aspirin-tolerant asthma patients. Generation of 15-HETE, prostaglandin E_2 (PGE_2), and leukotriene C_4 by unstimulated PBLs was similar between groups. Lipoxin A_4 production was reduced in the aspirin-sensitive group, 300 vs 690 pg/mL.

In response to incubation with aspirin, generation of 15-HETE increased in dose-dependent fashion only in the aspirin-sensitive group. Leukocytes from these patients also showed increased 15-HETE production in response to naproxen, but not indomethacin or specific cyclo-oxygenase-2 inhibitors such as celecoxib. The PGE_2 analog misoprostol inhibited the aspirin-induced increase in 15-HETE generation by PBLs from aspirin-sensitive patients. In contrast, in the aspirin-tolerant group, misoprostol led to increased aspirin-induced 15-HETE generation.

Specific aspirin-induced generation of 15-HETE may play a pathogenetic role in aspirin-sensitive rhinosinusitis-asthma, possibly through a mechanism involving 15-lipoxygenase. Cyclo-oxygenase-2 inhibitors have no effect on 15-HETE production. Misoprostol reduces aspirin-induced 15-HETE generation by leukocytes from aspirin-sensitive patients, but has the opposite effect in aspirin-tolerant asthma patients.

COMMENT: *Despite the well-recognized association of aspirin intolerance accompanied by hyperplastic rhinosinusitis and polyposis, the biochemical mechanism eludes us. This study suggests a central role for 15-HETE, which is produced in large amounts after aspirin challenge in vitro only by leukocytes from aspirin-sensitive subjects. The authors' theory--bear with me--is that aspirin inhibits PGE_2 production, which removes PGE_2 control of the enzyme 15-lipoxygenase in the respiratory mucosa, which then produces increased amounts of 15-HETE. We may be getting closer to understanding exactly where to intervene in this devastating disease.*
R. J. M.
Kowalski ML, Ptasinska A, Blenklewicz B, et al: Differential effects of aspirin and misoprostol on 15-hydroxyeicosatetraenoic acid generation by leukocytes from aspirin-sensitive asthmatic patients.
J Allergy Clin Immunol. 2003;112-505-512. ♦♦

Dietary Factors Affect Risk of Childhood Wheeze

THE possible effects of diet on asthma are a topic of debate, but few studies have looked at the relationship between diet and asthma in children. Dietary factors were studied for their impact on wheezing and allergic rhinitis in children.

The study included baseline data 5,257 Italian children, aged 6 to 7 years, from the International Study on Asthma and Allergies in Childhood. One-year follow-up data on respiratory symptoms were available for 4,104 children. Intake of various types of foods--including foods rich in antioxidants and those containing animal fats and omega-3 fatty acids-- was measured by a food frequency questionnaire.

Children with high intake of cooked vegetables, tomatoes, and fruit had lower rates of wheeze and short- ➤➤

ness of breath with wheezing. Citrus fruit consumption also had a protective effect against shortness of breath with wheezing. Bread and margarine were linked to an increased risk of wheeze, while bread and butter were linked to shortness of breath with wheezing. Consistent with the Italian diet, the children's intake of bread, butter, and margarine was low. Parental smoking was frequent.

These data in Italian children suggest that high consumption of vegetables and fresh fruit reduces the risk of wheezing, while consumption of butter and margarine has the opposite effect. The protective effects of citrus and other fruits may be related to their high levels of antioxidants. Despite the study limitations, the results suggest that a diet high in fruit and vegetables and low in fatty foods may reduce the risk of childhood wheeze.

COMMENT: *Diet and allergy have a long and often controversial relationship. While many accept the relationship as valid, specific food groups and their relationship to asthma activity have not been established. This retrospective study looked at the dietary habits of more than 5,000 Italian children to study patterns of asthma activity (questionnaire-derived) associated with specific food intake. The results showed that antioxidant-rich foods such as citrus fruit were protective against wheeze and dyspnea, while bread, butter, and margarine increased these risks. The data suggest a possible role for antioxidant-rich foods or supplements in the management of asthma.*
G. D. M.
Farchi S, Forastiere F, Agabiti N, et al: Dietary factors associated with wheezing and allergic rhinitis in children.
Eur Respir J. 2003;22:772-780.

Antihistamines for AOM Lead to Prolonged Middle Ear Effusion

MANY children with acute otitis media (AOM) have persistent effusion several months later, suggesting that treatment may need to do more than eliminate the causative bacteria. Classic H1-receptor antagonist antihistamines and corticosteroids have been used in AOM. The short- and long-term efficacy of adjunct therapy with antihistamine and/or corticosteroid was studied in children at high risk of recurrent AOM.

The trial included 198 children, aged 3 months to 6 years, who had AOM and were considered at risk for recurrent episodes. All received ceftriaxone, 50 mg/kg IM. They were also randomized to receive placebo; prednisolone, 2 mg/kg/d for 5 days; chlorpheniramine maleate, 0.35 mg/kg/d for 5 days; or both prednisolone and chlorpheniramine. Acute and long-term outcomes were compared.

The various treatment groups had similar clinical outcomes: overall treatment failure or relapse rate was 18%, while 6-month recurrence rates were 33% to 42%. Median duration of middle ear effusion was 73 days in children assigned to chlorpheniramine alone, compared with 23 to 36 days in the other three groups. Children receiving prednisolone were more likely to have temporary improvement of the tympanometric findings at 5 days. Side effects were similar among groups.

For children with AOM at high risk of recurrence, adding antihistamine and/or corticosteroid to antibiotic treatment does not improve short- or long-term outcomes. Adjunct antihistamine therapy appears to lead to a prolonged duration of middle ear effusion. This is an important adverse effect, because antihistamines are widely used in children with AOM or upper respiratory viral infections.

COMMENT: *It is not unusual for the young child who has otitis to be medicated by the parent with over-the-counter cold medications containing conventional H1 antihistamines. In this study, 5 days of chlorpheniramine not only did not improve the results of antibiotic treatment of otitis media, but was associated with prolonged middle ear effusion: double the number in the placebo group at 3 months. Considering that this may be an anticholinergic effect of chlorpheniramine, it would be valuable to know if a newer H1 antihistamine, such as loratadine or cetirizine (available in syrup for younger children), would avoid this side effect.*
J. A. A.
Chonmaitree R, Saeed K, Uchida T, et al: A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media.
J Pediatr. 2003;143:377-385.

Domestic Cleaners Have Higher Rate of Asthma

OCCUPATIONAL asthma has not traditionally been linked to cleaning work, but some studies have found an increased rate of asthma among cleaners. There is evidence that this risk is concentrated in domestic cleaners.

A random, population-based sample of 4,521 women, aged 30 to 65 years, living in the Barcelona metropolitan area were surveyed about their history of respiratory symptoms and of working as a cleaner. The presence of asthma was assessed on the basis of past-year symptoms or current use of asthma medications.

The survey response rate was 90%. Thirteen percent of the women were currently working as domestic cleaners while another 26% had done so in the past. On logistic regression analysis, current employment as a domestic cleaner was associated with an increased prevalence of asthma--odds ratio 1.46--compared to women who had never worked as cleaners. For women with a previous history of domestic cleaning work, the risk was even higher, odds ratio 2.09. Women working as cleaners in offices or other nondomestic settings, currently or in the past, were not at increased risk.

The results suggest an increased prevalence of asthma among women working as domestic cleaners. The authors estimate that 25% of all cases of asthma among the women surveyed can be attributed to domestic cleaning. The exact exposures leading to this increased asthma risk are unknown. ➤➤

COMMENT: *Work-related exposures are estimated to cause a significant number of adult asthma cases. This cross-sectional study in Spain revealed that employment in domestic cleaning may induce or aggravate asthma. However, office cleaners did not show an excess risk for either asthma or chronic bronchitis. Although the specific causative mechanism was not addressed in the study, one wonders whether domestic workers are exposed to significant quantities of indoor allergens. Further studies will be required to isolate specific causative agents.*
E. J. B.
Medina-Ramón M, Zock JP, Kogevinas M, et al: Asthma symptoms in women employed in domestic cleaning: a community based study.
Thorax. 2003;58:937-941.

REVIEWS OF NOTE

COMMENT: *Allergists are seeing more patients with sleep apnea. This concise review highlights the pathophysiology, clinical consequences, and therapeutic options for this condition. Continuing medical education credit is available after answering the questions online.*
S. M. F.
Qureshi A, Ballard RD: Obstructive sleep apnea.
J Allergy Clin Immunol. 2003;112:643-651. ♦♦

COMMENT: *This position paper by the EAACI interest group updates the clinician on revisions of past diagnostic guidelines for evaluation of allergic reactions to beta-lactams.*
E. J. B.
Torres MJ, Blanca M, Fernandez J, et al: Diagnosis of immediate allergic reactions to beta-lactam antibiotics.
Allergy. 2003;58:961-972. ♦♦

COMMENT: *Occupational asthma (OA) is a problem increasingly recognized by allergists. Therapy largely involves control of exposure and usually standard asthma-based medications. Prevention of OA is often thought of as impractical or even impossible. This provocative review defines OA in several contexts, describes obstacles to prevention strategies, and reviews the literature for results of OA prevention. Considering the points made in this review may provide further validation of the need for allergists-immunologists in the management of industrial airway diseases.*
G. D. M.
Cullinan P. Tarlo S, Nemery B: The prevention of occupational asthma.
Eur Respir J. 2003;22:853-860. ♦♦

COMMENT: *There is continuing controversy over whether inhaled corticosteroids are beneficial in COPD. This comprehensive meta-analysis suggests that inhaled steroids significantly slow the rate of decline in FEV_1 in patients with COPD. However, the effect is quantitatively small.*
E. J. B.
Sutherland ER, Allmers H, Ayas NT, et al: Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis.
Thorax 2003;58:937-941. ♦♦

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