AllergyWatch®

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

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Good News for Dogs (and Other Indoor Pets)

PREVIOUS studies have suggested that early-childhood exposure to pets may reduce the risk of later allergic sensitization. However, there are still no clear data to guide advice as to how keeping pets will affect the risk of childhood allergies. The relationship between early-childhood pet exposure and allergic sensitization at age 18 was analyzed using data from a birth cohort study.

The analysis included data on 565 participants from the Childhood Allergy Study, all born in the Detroit area from 1987 to 1989. At age 18, the participants underwent measurement of serum total IgE and specific IgE for dust mite, cat, dog, ragweed, timothy grass, *Alternaria* spp, and peanut. Any specific IgE level of 0.35 kU/L or higher was defined as atopy. Exposure to indoor pets--including first-year, cumulative lifetime, and at specific ages--was assessed from interviews with parents during childhood.

The likelihood of atopy at age 18 was unrelated to exposure to indoor cats and dogs during the first year of life. Among 18-year-olds with atopy, those who lived with pets during the first year of life had a dose-dependent reduction in total serum IgE. There were no consistent associations between total or specific IgE and cumulative or age-specific pet exposure. Youth exposed to two or more pets in the first year of life tended to have a lower sensitization rate than those exposed to no pets.

Early-life exposure to indoor pets does not significantly increase or decrease the likelihood of sensitization to common allergens at age 18. Among adolescents with atopy, those with early exposure to pets may have lower total IgE levels. No significant associations are noted for overall pet exposure during childhood or exposure at specific ages.

COMMENT: *Parents frequently ask if they should remove the family pet to help reduce the likelihood that their children will develop allergies. Re-examining the data from patients in the Childhood Allergy Study, this study reports specific IgE data in those children at* ➤➤

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

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

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18 years of age. Although pet exposure in the first year of life was once again associated with reduced atopy, overall cumulative exposure to the pets did not strongly correlate with developing atopy. It looks like Fido can stay; score one for the hygiene hypothesis.
S.M.F.
Wegienka G, Johnson CC, Havstad S, et al: Indoor pet exposure and the outcomes of total IgE and sensitization at age 18 years.
J Allergy Clin Immunol. 2010;126:274-279. ♦♦

THERE is evidence that exposure to animals during early life, and even during gestation, affects the development of the human immune system. However, the mechanisms of this effect and the specific exposures involved are unclear. This study assessed the relationship between exposure to animals and early immune development in children.

The study included 228 Finnish mother-child pairs from a birth cohort study. Cord blood samples were available from all infants, and peripheral venous blood samples collected at age 1 from 200 infants. The samples were stimulated with gram-positive superantigen staphylococcal enterotoxin B, gram-negative bacterial lipopolysaccharide (LPS), and a combination of mitogenic phorbol 12-myristate 13-acetate and calcium ionophore ionomycin (P/I). Cytokine responses to stimulation--including tumor necrosis factor (TNF)-α, interferon (IFN)-γ,interleukin (IL)-5, IL-8 and IL-10--were compared with data on the children's history of exposure to animals.

At birth, children born to parents with a dog in the home had decreased TNF-α-producing capacity. The median response to P/I stimulation of cord blood was 841 vs 881 pg/10^6 WBC for dog ownership vs non-ownership. The difference remained significant in 1-year blood samples: 1,290 vs 1,530 pg/10^6 WBC. A significant association was also noted for response to LPS stimulation.

Both associations remained significant with adjustment for potential confounders. Cat ownership had no effect on cytokine responses.

Dog ownership is associated with reduced innate immune responses in infants, which may be evident even at birth. The reported reductions in cytokine production could help to prevent exaggerated immune responses to harmless antigens later in life. The findings may help to explain the mechanism by which early-life exposure to dogs affects human immune system development.

COMMENT: *Pet exposure early in life has been reported to alter the risk of developing allergies, although sorting out how immunological pathways are affected by pets has been challenging. This study looked at the profile of mitogen-stimulated cytokine production at birth and at 1 year of age. The TNF-α response was significantly lower in infants living in homes with a dog, while there was no difference in the responses of other candidate cytokines such as IFN-γ, IL-5, IL-8, or IL-10. The authors speculate that early exposure to dog reduces innate immune responses in a way that prevents allergies later in life.*
Lappalainen MHJ, Huttunen KL, Roponen M, et al: Exposure to dogs is associated with a decreased tumour necrosis factor-α producing capacity in early life.
S.A.T. ♦♦

Asthma Risk Increased with Both Allergic and Nonallergic Rhinitis

STUDIES have shown an increased rate of asthma in adolescents and adults with allergic or nonallergic rhinitis. Data from a prospective cohort study were used to compare the prevalence of asthma and other allergic disease outcomes in 7-year-old children with allergic vs nonallergic rhinitis.

The analysis included three groups of children from the Copenhagen Prospective Study on Asthma in Childhood: 38 with allergic rhinitis, 67 ➤➤

with nonallergic rhinitis, and 185 without rhinitis. Asthma prevalence was compared among groups. Intermediary endpoints included eczema, food sensitization, filaggrin null-mutations, total IgE, blood eosinophil count, exhaled nitric oxide, lung function, and bronchial responsiveness.

Asthma prevalence was 21% in children with allergic rhinitis and 20% in those with nonallergic rhinitis, compared to 5% for children without rhinitis. A number of other allergic disease outcomes were also increased for children with allergic rhinitis compared to controls, including food sensitization, 47% vs 13%; eczema, 66% versus 43%; and bronchial hyperresponsiveness, 23% vs 9%. None of these other outcomes were more frequent in children with nonallergic rhinitis, compared to children without rhinitis.

Children with allergic rhinitis also had higher total IgE, 155 vs 41 kU/L; higher blood eosinophil count, 0.46 vs 0.30 x 10^9/L; and higher exhaled NO, 15.9 vs 6.6 ppb. Children with allergic rhinitis were three times more likely to have filaggrin null-mutations, but this did not modify the other associations.

In 7-year-old children, allergic and nonallergic rhinitis are associated with similar increases in asthma prevalence. This finding supports the concept of an association between the upper and lower airway, independent of allergy-related inflammation. Bronchial hyperresponsiveness and increased exhaled NO are found only in children with allergic rhinitis.

COMMENT: *The concept of the "unified airway," suggesting that lower airway disease is linked to nasal pathology, has been popular recently. These Danish researchers report data from a large prospective birth cohort, which suggests that reactive airways disease is present in children with both allergic and nonallergic rhinitis. Those children with allergic rhinitis and asthma also had higher exhaled NO than children who had allergic rhinitis without asthma. The authors suggest that different endotypes of asthma are responsible for this phenomenon.*
S.M.F.

Chawes BLK, K Bønnelykke, Kreiner-Møller E, Bisgaard H: Children with allergic and nonallergic rhinitis have a similar risk of asthma.
J Allergy Clin Immunol. 2010;126:567-573. ♦♦

FEF_{25-75} Provides Useful Information in Childhood Asthma

UNDER current guidelines, evaluation of forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) does not play an important role in clinical evaluation of airflow limitation. However, some reports suggest that FEF_{25-75}, as well as the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) can provide information that FEV_1 alone does not. This study assessed the additional information provided by FEF_{25-75} in children with asthma.

The study was a secondary analysis of 479 children, aged 6 to 17 years, with mild to moderate asthma enrolled in two multicenter clinical trials of controller medications. Correlation analyses were performed to determine whether measurement of FEF_{25-75} provided useful information beyond that provided by gold- standard measurement of FEV_1.

Of the 479 children, 437 had a normal FEV_1 percent predicted. In this group, FEF_{25-75} percent predicted and FEV_1/FVC percent predicted were positively correlated with $\log_2$ methacholine PC_{20} and with morning and evening peak expiratory flow percent predicted. Both measures were negatively correlated with $\log_{10}$ fraction of exhaled nitric oxide and bronchodilator responsiveness. Of the three pulmonary function measures, FEF_{25-75} percent predicted was most strongly correlated with bronchodilator responsiveness and $\log_2$ methacholine PC_{20}. On receiving operating characteristic curve analysis, an FEF_{25-75} of 65% predicted was 90% sensitive and 67% specific in detecting a 20% increase in FEV_1 in response to albuterol.

The FEF_{25-75} percent predicted is a good indicator of bronchodilator responsiveness in children with mild to moderate asthma and normal FEV_1. This measure can show airway dysfunction that is not reflected by FEV_1 alone, and should be evaluated in clinical studies of childhood asthma.

COMMENT: *This report uses elegant statistical analysis to assess the potential usefulness of FEF_{25-75} in predicting bronchodilator responsiveness in children with asthma who have normal FEV_1. We currently use FEV_1 and the FEV_1/FVC ratio to evaluate control in asthmatic children. Mid-maximal flow rates are less effort-dependent and measure airflow through smaller airways. This study suggests that children with low FEF_{25-75} may have treatable, reversible airway obstruction in spite of normal FEV_1 and FEV_1 /FVC ratio values. The authors suggest that FEF_{25-75} should be included in assessment of childhood asthma control.*
S.M.F.

Simon M, Chinchilli V, Phillips BR, et al: Forced expiratory flow between 25% and 75% of vital capacity and FEV_1/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV_1 values.
J Allergy Clin Immunol. 2010;126:527-534. ♦♦

H1N1 Vaccine Is Safe for Most Patients with Egg Allergy

THE egg content of influenza vaccine poses some risk of anaphylactic reactions in patients with egg allergy. A Canadian experience with adjuvanted 2009 pandemic influenza A/H1N1 vaccination in egg-allergic patients is reported.

The experience included 1,076 patients with egg allergy undergoing vaccination to prevent pandemic H1N1 influenza. Of these, 830 had confirmed egg allergy. Patients with a history of respiratory or cardiovascular reactions to egg received the vaccine in divided doses: 10% at first, followed by the remaining 90% after 30 minutes. Children and other groups of egg-aller-➤➤

gic patients received the vaccine in a single dose. All patients were observed for 60 minutes, with a phone call at 24 hours to evaluate possible delayed reactions.

Just 9% of patients met criteria for divided dosing. There were no anaphylactic reactions. Minor reactions were treated with an antihistamine in 9 patients; 8 of these reactions occurred after 1 hour. Another 3 patients were treated with salbutamol. In a series of 3,600 children with reported egg allergy, there were no cases of anaphylaxis meeting Brighton Collaboration criteria, although 2 patients were treated with epinephrine for possible allergic symptoms.

This study reports no cases of anaphylaxis resulting from H1N1 vaccine in a series of patients with confirmed egg allergy. Although further studies with seasonal vaccines are needed, the risk of anaphylaxis after influenza vaccination in egg-allergic patients appears small.

COMMENT: *These Canadian researchers used last year's H1N1 pandemic as an opportunity to collect data on 1,076 patients with egg allergy who needed to be vaccinated with the H1N1 influenza vaccine. Those who had a history of the equivalent of a grade 4 anaphylactic reaction to egg received two doses of vaccine while all others received the full dose. Only 17 patients had minor allergic reactions within 24 hours after vaccination, and none had anaphylaxis. This report adds to the growing literature supporting the safety of egg-based vaccine administration in egg-allergic patients.*
S.M.F.

Gagnon R, Primeau MN, Des Roches A, et al: Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine.
J Allergy Clin Immunol. 2010;126:317-322. ♦♦

Smaller Families Can't Explain Rise in Atopy

THE reasons for the rising prevalence of allergic disease remain unclear. There is a known inverse association between birth order and the risk of respiratory allergic disease, and the increase in allergies disease has been accompanied by decreasing fertility rates.

The association between temporal changes in family size and the prevalence of atopy was evaluated by a meta-analysis of data from 5 U.K. studies of the effects of birth order on atopy risk. The studies were compared with statistics on changes in U.K. family size from the 1960s to the 2000s.

Based on the pooled data, odds ratios for atopy were 0.90 for second-born children, 0.69 for third-born children, and 0.69 for fourth-born and subsequent children. When expected increases in atopy across the decades were calculated, the expected relative increase in prevalence resulting from changes in family size from 1960 to 2001 was only 3%.

This meta-analysis confirms the strong association between birth order and atopy. However, the decrease in family sizes since the 1960s does not appear to be a major contributor to the increased prevalence of atopy.

COMMENT: *Multiple studies have shown an inverse relationship between birth order and risk of atopy. This retrospective study analyzed data from five separate epidemiologic studies in order to calculate, for a given birth order category, the relative risk of being atopic in 2001 compared with 1960. The authors concluded that shrinking family size probably accounts for only 3% of the more than 20% increase in prevalence of atopy since 1960.*
S.A.T.

Upchurch S, Harris JM, Cullinan P: Temporal changes in UK birth order and the prevalence of atopy.
Allergy. 2010;65:1039-1041. ♦♦

Teens with Food Allergy: A Disaster Waiting To Happen

AMONG patients with nut allergy, the risk of fatal anaphylaxis peaks in adolescence and young adulthood. Adolescents warrant special attention in the allergy clinic, as they assume primary responsibility for managing their own condition. This qualitative study examined the practical challenges faced by teenaged patients with food allergies.

The investigators performed and analyzed semi-structured interviews with 18 British teenagers with food allergies. The patients were 10 females and 8 males, median age 15 years; all had allergy to peanut or tree nuts.

Analysis identified three main themes: allergen avoidance, preparing for reactions, and treating reactions. Most of the participants reported consuming foods labeled "may contain" the offending food, as they believed these products were very unlikely to contain allergen. Many of the teens said they generally carried their epinephrine injector only when they thought they were at particularly high risk of a reaction. A minority of participants did not know how to treat an allergic reaction, including how to perform epinephrine self-injection. Most felt that educating other students at their school about the seriousness of food allergies would help them to live with their condition.

Many adolescents with food allergies exhibit risky behaviors, such as consuming foods that could contain allergen and not carrying epinephrine. The findings have implications for food labeling and for public education regarding food allergies.

COMMENT: *The number or teenagers with life-threatening food allergies is on the rise, and this age group is well known to have an increased risk of exposure to the allergenic food. This study interviewed teens with food allergies in order to better understand why their risk is so high. It turns out that the majority of teens admitted eating foods labeled "may contain" the offending allergen. Many also admitted not carrying their injectable epinephrine except when they anticipated a higher risk of exposure. The teens also felt that it would help to educate their peers about the seriousness of food allergies.*
S.A.T. ➤➤

Monks H, Gowland MH, Mackenzie H, et al: How do teenagers manage their food allergies?
Clin Exp Allergy. 2010;40:1533-1540. ♦♦

Adult-Onset Asthma: Usually Not Atopic

NEW-ONSET asthma commonly affects adult patients. Although some studies have reported on risk factors, there are few data on atopy and other determinants of this condition. Long-term follow-up data were used to assess the contribution of atopy and other risk factors to adult-onset asthma.

The analysis included 4,588 participants in the European Community Respiratory Health Survey. All reported that they had never had asthma at a baseline survey in 1990-95, when they were 20 to 44 years old.

At a follow-up survey in 1998-2003, 179 participants had developed new-onset asthma: a rate of 4.5 per 1,000 person-years. On logistic regression, risk factors for adult-onset asthma were female sex, odds ratio (OR) 1.97; bronchial hyperresponsiveness, OR 3.25; atopy, OR 1.55; FEV_1 less than 100% of predicted, OR 1.87; nasal allergy, OR 1.98; and maternal asthma, OR 1.91. Other risk factors that were possible but unconfirmed included obesity, early-life respiratory infections, and high-risk occupations.

Among adults with atopy, independent risk factors for asthma were total IgE level and sensitization to cat. The researchers estimated that 12% to 21% of new-onset adult asthma was attributable to atopy.

These longitudinal data show a substantial risk of new-onset asthma in middle-aged adults with no previous history of asthma. Several risk factors are identified, notably including reduced pulmonary function. However, atopy does not appear to be a major contributor to new-onset adult asthma.

COMMENT: *The concept of adult-onset "intrinsic" asthma is certainly not new, though in recent years there has not been much new information about it. This large longitudinal survey study reports 179 new cases of asthma out of 4,588 middle-aged adult participants over a 9-year period. Fewer than 20% were atopic. Other risk factors included being female, maternal asthma, abnormal baseline spirometry, and bronchial hyperresponsiveness. Obesity, occupational factors, and respiratory infections early in life also increased risk. It is important for asthma specialists to be aware of this phenotype in order to optimize diagnostic testing and management strategies.*
S.A.T.
Antó JM, Sunyer J, Basagaña X, et al: Risk factors of new-onset asthma in adults: a population-based international cohort study.
2010;65:1021-1030. ♦♦

Few Data Support Corticosteroids for Acute Anaphylaxis

EPINEPHRINE is the mainstay of treatment for anaphylaxis. After initial treatment, many patients receive glucocorticoids. Some recent studies have even reported that patients are more likely to receive corticosteroids than epinephrine as their initial treatment for anaphylaxis. A Cochrane systematic review was performed to analyze evidence corticosteroids for treatment of anaphylaxis.

A comprehensive review was performed to identify randomized or quasi-randomized controlled trials comparing corticosteroids with any treatment--placebo, epinephrine, and/or antihistamine--for anaphylaxis. Of a total of 2,496 papers identified in the initial search, none were randomized or quasi-randomized trials. There were also no planned or ongoing trials that met the search criteria.

There is little research support for the use of corticosteroids to treat anaphylaxis. While acknowledging the difficulty of performing randomized trials of this issue, the authors outline some of the key issues to be considered.

COMMENT: *Retrospective studies have shown that emergency departments are more likely to administer systemic corticosteroids than epinephrine to patients experiencing anaphylaxis. This Cochrane review from the United Kingdom identified 2,496 anaphylaxis studies in an attempt to assess the evidence supporting this approach. In fact, none of the studies met the authors' criteria for "randomized or quasi-randomized controlled trial" The authors do not argue that corticosteroid treatment should be removed from anaphylaxis treatment algorithms, but rather that there should be a more explicit disclaimer about how little evidence exists in support of this treatment.*
S.A.T.
Choo KJL, Simons E, Sheikh A: Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review.
Allergy. 2010;65:1205-1211. ♦♦

Smoking Ban Leads to Reduced Admissions for Childhood Asthma

SMOKE-FREE laws have been reported to lead to reduced respiratory symptoms among workers in bars. The effects on respiratory health in people without occupational exposure to environmental tobacco smoke are unknown. Changes in hospitalizations for pediatric asthma were analyzed after smoke-free legislation in Scotland.

A ban on smoking in enclosed public places and workplaces in Scotland was implemented in March, 2006. Scottish hospital data were reviewed to ascertain rates of asthma hospitalization among children under age 15 from 2000 to 2009, adjusted for age, sex, socioeconomic status, urban versus rural residence, and month and year of admission.

Before the smoke-free legislation, asthma hospitalizations in children were rising: mean increase 5.2% per year from 2000 to 2006. After the smoking ban, admissions for childhood asthma decreased sharply, mean decrease 18.2% per year. With adjustment for potential confounders, there was still a net reduction of 15.1% per year. The reduction was significant for both ➤➤

preschool- and school-aged children.

A ban on public smoking may lead to reduced hospitalizations for childhood asthma. The findings provide evidence that smoke-free legislation can reduce respiratory disease even in populations without occupational exposure to environmental tobacco smoke.

COMMENT: *Legislation banning smoking in public places has been well-received by most people--even smokers--and especially by those with lung diseases like asthma. But can we measure the benefits? Smoke-free legislation was implemented in Scotland in 2006. This study shows that right after that date, the rate of hospitalization of preschool and school-aged children in that country declined substantially. But how can that be, since children typically don't frequent restaurants and bars? The authors contend that voluntary restrictions on smoking in homes also increased after the legislation regulating public places was passed. For a change, an unintended consequence of legislation may have been quite positive! The study can't completely rule out other factors like social or financial disincentives, but it is interesting speculation.*
R.J.M.

Mackay D, Haw S, Ayres JG, et al: Smoke-free legislation and hospitalizations for childhood asthma.
N Engl J Med. 2010;363:1139-1145. ♦♦

Tiotropium Step-Up Therapy is Effective in Uncontrolled Asthma

IN patients with inadequate control of asthma symptoms on low- to medium-dose inhaled corticosteroids (ICS), options for step-up therapy include increasing the dose of ICS or adding a long-acting beta-agonist (LABA). The role of anticholinergic agents such as tiotropium bromide is unclear. This randomized trial compared tiotropium with double-dose ICS and add-on LABA as step-up therapy for uncontrolled asthma.

The study included 210 asthma patients with inadequate disease control on inhaled beclomethasone, 80 µg twice daily. They were randomly assigned to receive tiotropium or salmeterol added on to ICS, or a doubled dose of ICS. Pulmonary function and symptom scores were compared between groups.

Compared to a doubled-dose of ICS, tiotropium add-on therapy was associated with a greater improvement in morning and evening peak expiratory flow: mean difference 25.8 and 35.3 L/min, respectively. Tiotropium plus ICS also yielded small but significant differences in proportion of asthma-control days, prebronchodilator FEV_1, and asthma symptom score.

For all outcomes measured, add-on tiotropium was noninferior to add-on salmeterol. Tiotropium had a greater effect on prebronchodilator FEV_1. Responses were also similar on analysis of patients with characteristics similar to those in studies used to establish the clinical efficacy of LABA therapy.

Adding tiotropium to ICS improves symptoms and pulmonary function in patients whose asthma is inadequately controlled with ICS alone. The effect is similar to that of add-on LABA therapy, both of which are superior to a doubled dose of ICS. The results provide "clinical equipoise" for larger studies of tiotropium for asthma control.

COMMENT: *When asthma isn't sufficiently controlled on ICS, the clinician may double the dose of the ICS or add a LABA. This study included 210 patients who were, on average, allergic adults with long-standing asthma, and compared the results of doubling the ICS, adding salmeterol, or adding inhaled tiotropium. They found that doubling of the ICS was the least effective strategy, and that adding tiotropium was similar ("noninferior") to adding salmeterol. In the United States, tiotropium is approved for chronic obstructive pulmonary disease but not asthma. In time, maybe it will be.*
R.J.M.

Peters SP, Kunselman SJ, Icitovic N, et al: Tiotropium bromide step-up therapy for adults with uncontrolled asthma.
N Engl J Med. 2010;363:1715-1726. ♦♦

Hereditary Angioedema: Three New Treatments

PATIENTS with hereditary angioedema (HAE) experience acute, intermittent, and potentially life-threatening attacks of edema involving the skin and mucosa. The disease results from mutations causing reduced activity or quantity of C1 esterase inhibitor, a major inhibitor of plasma kallikrein and coagulation factor XIIa. The recombinant protein ecallantide is a potent, specific inhibitor of kallikrein. A phase 3 trial of ecallantide for treatment of HAE attacks is reported.

The multicenter trial included 72 patients with acute attacks of HAE. One group received ecallantide, 30 mg sc, while the other group received placebo. Outcomes were assessed on a patient-rated score ranging from +100 (significant improvement) to -100 (significant worsening) and the mean symptom complex severity score, with a range from +2 (mild symptoms at baseline to severe symptoms after treatment) to -3 (from severe symptoms to no symptoms).

At 4 hours, the median treatment outcome score was 50.0 with ecallantide versus 0.0 with placebo. Median change in the mean symptom complex severity score was -1.00 versus -0.50, respectively. Estimated time to onset was 165 min with ecallantide vs 240 min with placebo. There were no serious adverse events.

The kallikrein inhibitor ecallantide is an effective treatment for acute attacks of HAE. At 4 hours after treatment, patient-rated outcomes are significantly better with ecallantide than with placebo. Further studies are needed to compare ecallantide with active control treatments.

IN patients with HAE, reduced activity of C1 esterase may lead to elevated levels of bradykinin, the key mediator of HAE symptoms. The selective bradykinin B2 receptor antagonist icatibant was evaluated as a ➤➤

treatment for acute HAE attacks.

The authors report on two double-blind, randomized trials of icatibant for HAE patients with cutaneous or abdominal attacks. In the "For Angioedema Subcutaneous Treatment" 1 (FAST-1) trial, 56 patients were assigned to treatment with icatibant, a single dose of 30 mg sc, or placebo. Median time to clinically significant symptom relief was 2.5 hours with icatibant vs 4.6 hours with placebo. Rescue medication was needed by 3 patients in the icatibant group vs 13 in the placebo group.

In the FAST-2 trial, 72 patients were assigned to treatment with icatibant or with oral tranexemic acid, 3 g/d for 2 days. Median time to significant symptom relief was 2.0 vs 12.0 hours, respectively. In both studies, time to initial symptomatic improvement was faster with icatibant, as rated by both patients and investigators. There were no serious adverse events related to icatibant.

The bradykinin B2 receptor antagonist icatibant is a beneficial treatment for acute HAE attacks. This includes comparison with tranexemic acid as an active control. Early use of rescue medication may have partially obscured the benefit of icatibant vs placebo.

HEREDITARY angioedema is caused by mutations of the C1 inhibitor gene, causing low levels or low activity of C1 inhibitor. This paper reports on two randomized trials evaluating a new nanofiltered C1 inhibitor concentrate for the treatment and prevention of acute HAE attacks.

In the treatment trial, 68 patients were given nanofiltered C1 inhibitor concentrate, one or two IV injections of 1,000 U, or placebo for the treatment of angioedema attacks. Median time to "onset of unequivocal relief" was 2 hours in patients receiving the C1 inhibitor concentrate vs more than 4 hours in the placebo group.

The prevention study was a crossover trial in which 22 patients with HAE received prophylactic nanofiltered C1 inhibitor concentrate (twice-weekly injections of 1,000 U) or placebo during two 12-week periods. Mean number of attacks per 12-week period was 6.26 with C1 inhibitor concentrate vs 12.73 with placebo. Prophylactic C1 inhibitor concentrate was also associated with reduced duration and severity of attacks, less need for rescue therapy, and fewer days with swelling.

Nanofiltered C1 inhibitor concentrate is effective for the treatment and prevention of HAE attacks. This treatment can shorten the time to symptom relief in patients with acute attacks, and reduce the frequency and severity of attacks when used prophylactically.

COMMENT: *Hereditary angioedema is an autosomal dominant disorder limiting production of C1 inhibitor, and can cause life-threatening edema of skin and mucosal tissues. It is mediated by the bradykinin pathway and therefore, unlike allergic angioedema, HAE is not responsive to epinephrine or antihistamines. In recent years, three competing treatments have been developed. Ecallantide inhibits plasma kallikrein; icatibant is a bradykinin receptor antagonist; C1 inhibitor concentrate is purified from human plasma.*

In August 2010, the New England Journal of Medicine *published one study of each of these agents. As yet, there has been no published head-to-head comparative trial. There are distinct differences in mechanism and administration. Each agent was effective against acute attacks to some degree. Used prophylactically, the C1 inhibitor concentrate reduced the frequency of acute attacks.*

R.J.M.

Cicardi M, Levy RJ, McNeil DL: Ecallantide for the treatment of acute attacks in hereditary angioedema. **N Engl J Med**. 2010;363:523-531.

Cicardi M, Banerji A, Bracho F: Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. **N Engl J Med**. 2010;363:532-541.

Zuraw BL, Busse PJ, White M: Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. **N Engl J Med**. 363:513-522.

♦♦

Pollutant Exposure at School Affects Childhood Asthma

INCREASES in the prevalence of asthma and allergies in recent decades have been accompanied by increased levels of traffic-related air pollution in industrialized countries. Short-term exposure to urban air pollution has been shown to exacerbate existing asthma. This study sought to clarify the long-term effects of exposure to urban air pollution on asthma and allergies in school-aged children.

The study used a validated dispersion model of exposure to urban air pollution, incorporating data on traffic conditions, topography, meteorology, and background pollution. This model was used to create 3-year averaged concentrations of major air pollutants for 108 schools in 6 French communities, chosen for contrasting air quality. The pollution exposure data were compared with information on reported asthma and allergies, skin prick test results, and exercise-induced asthma for 6,683 children, aged 9 to 11, at those schools.

The final analysis included 4,907 children who had lived at their current address for the preceding 3 years. Lifetime asthma, asthma in the past year, and exercise-induced asthma were positively associated with several air pollutants: benzene, SO_2, particulate pollutants with a 50% cutoff aerodynamic diameter of 10 µm (PM_{10}), nitrogen dioxides (NO_x), and CO. Lifetime and past-year eczema were positively related to benzene, PM_{10}, NO_2, NOx, and CO. Lifetime allergic rhinitis was related to PM_{10}, while pollen sensitization was related to benzene and PM_{10}.

On analysis of 2,213 children living at the same address since birth, lifetime asthma was associated with benzene, adjusted odds ratio (OR) per interquartile range 1.3, and PM_{10}, OR 1.4. Pollen sensitization was associated with volatile organic compounds and PM_{10}: OR 1.3 and 1.2, respectively.

Long-term exposure to urban air pollutants at school is associated with asthma and other allergic disease in children. The associations are strongest for PM_{10} and benzene, which are primarily emitted by traffic. ➤➤

The use of a dispersion model that captures small-scale variations in pollutant exposure is an important strength of this study.

COMMENT: *This large study of 4,907 children who had a stable address for 3 years shows that exposure to urban air pollution is a significant risk factor for lifetime asthma. This is highly significant in the location of neighborhood schools near heavily traveled roads, where significant exposure occurs nine months out of the year. Exposure to high levels of diesel exhaust particles are is of special concern, as this has been shown to enhance IgE-mediated inhalant allergy.*
B.E.C.
Pénard-Morand C, Raherison C, Charpin D, et al: Long-term exposure to close-proximity air pollution and asthma and allergies in urban children.
Eur Respir J. 2010;36:33-40. ♦♦

Ambient Pollutants Affect Childhood Asthma ED Visits

AMBIENT air pollution has been linked to asthma exacerbations, particularly in children. Further study is needed to clarify the dose-response and pollutant lag effects, as well as types of pollutants beyond those most commonly studied. Short-term associations between ambient air pollutant levels and emergency department (ED) visits for childhood asthma were studied.

The analysis included data on 91,386 visits to 41 Atlanta-area EDs for asthma by children aged 5 to 17 between 1993 and 2004. Rates of ED visits were compared with ambient concentrations of gaseous and particulate pollutants, measured by stationary monitors. The measurements included the components of particulate matter less than 2.5 µm in aerodynamic diameter ($PM_{2.5}$). Associations between ambient air pollutants and pediatric ED visits for asthma and wheezing were assessed, with separate rate ratios for the warm vs cold season.

As concentrations of ozone and traffic-related air pollutants increased, so did the rate of ED visits for asthma and wheezing. These two classes of pollutants continued to show independent effects in multipollutant models. On analysis of lag times, the effects of pollutants tended to be greatest on the day of the ED visit. These same-day associations were noted at relatively low ambient pollutant levels. Ozone was related to ED visits during both the cold and warm season, while several traffic-related pollutants showed significant effects during the warm season.

This large, single-city study shows that ambient levels of ozone and primary pollutants from traffic sources are independently associated with ED visits for asthma and wheezing in children. Significant associations are observed at relatively low ambient pollutant levels, underscoring the need for continued evaluation of national air quality standards.

COMMENT: *This large population study from Atlanta shows that both ozone and primary pollutants from traffic sources independently contribute to the burden of pediatric emergency department visits for asthma. The highest magnitude of concentrations was seen on the day of the ED visit, and this occurred at relatively low ambient concentrations. The higher density occurred during warm months when children were playing outside a larger percentage of the time. The same group has also shown that during the Olympics in Atlanta when urban traffic was significantly decreased, ED visits for asthma likewise decreased.*
B.E.C.
Strickland MJ, Darrow LA, Klein M, et al: Short-term associations between ambient air pollutants and pediatric asthma emergency department visits.
Am J Respir Crit Care Med. 2010;182:307-361. ♦♦

Swimming during Infancy May Increase Bronchiolitis Risk

SWIMMING in chlorinated pools is a possible risk factor for lower respiratory tract infection in infants. By increasing the risk of bronchiolitis, exposure to swimming pools could also increase the risk of asthma and allergic disease. Swimming in indoor and outdoor chlorinated pools during infancy was evaluated as a risk factor for bronchiolitis and its risk factors.

The parents of 430 kindergarten children completed a questionnaire regarding their child's health, including asthma and bronchiolitis; history of swimming pool use during infancy and childhood; and potential confounding factors. Children who had swum in indoor or outdoor chlorinated pools at any time before age 2 were at increased risk of bronchiolitis. The prevalence of bronchiolitis among children who swam as infants was 36.4%, compared to 23.8% in controls: odds ratio (OR) 1.68.

This association remained significant, and was even strengthened, after exclusion of other risk factors. On analysis excluding children with parental history of atopy and day-care attendance, the odds of bronchiolitis were more than four times higher for children who spent more than 20 hours in chlorinated pools during infancy. Children who attended chlorinated pools during infancy and developed bronchiolitis were at increased risk of asthma and respiratory allergies later in childhood.

Infants exposed to chlorinated swimming pools are at increased risk of bronchiolitis, and thereafter at increased risk of asthma and other respiratory allergic diseases. The association is significant for both indoor and outdoor pools and independent of other bronchiolitis risk factors. Although the mechanism is unknown, the irritant effects of chlorine may render the infant airway more sensitive to infection.

COMMENT: *The debate continues regarding the effect of indoor and outdoor chlorinated pools and the association between bronchiolitis and asthma. An association has again been shown in a group of young children exposed before 2 years of age--even in children who do not have a strong family history of asthma or allergic disease and have not attended daycare.* ➤➤

The association was significant for children who spent 20 hours in chlorinated pools during the first 2 years of life and was seen throughout childhood. The plausible explanation is that the infants' airways may be sensitized by the byproducts of chemicals used to retard bacterial and fungal growth. These airways could then be more susceptible to rhinovirus infection and increased airway inflammation. It should also be noted that Olympic swimmers, along with hockey players and cross-country skiers, have the highest incidence of exercise-induced bronchospasm.
B.E.C.
Voisin C, Sardella A, Marcucci F, Bernard A: Infant swimming in chlorinated pools and the risks of bronchiolitis, asthma and allergy.
Eur Respir J. 2010;36:41-47. ♦♦

High Rate of Suboptimal Asthma Control in General Pediatric Population

REGULAR assessment of disease control is a key part of guidelines for managing childhood asthma. Despite previous studies, the prevalence of uncontrolled childhood asthma remains unclear. A validated screening test was used to assess asthma control in a representative sample of pediatric primary care patients with asthma.

The cross-sectional survey study included 2,429 children aged 4 to 17 with self-reported (or parent-reported) asthma, seen at 29 U.S. pediatric offices. The mean age was 9.2 years; 52% were Hispanic or African American. All patients were evaluated using the Asthma Control Test (ACT) or Childhood Asthma Control Test (C-ACT). A score of 19 or less on either validated test indicated uncontrolled asthma.

Overall, 46% of the children had uncontrolled asthma, including 54% of those seeing the pediatrician for respiratory complaints and 35% for other problems. Over the past year, at least one asthma exacerbation had occurred in 50% of children with uncontrolled asthma vs 33% of those with controlled asthma. Uncontrolled asthma was also associated with more missed school days and more missed work days for parents. For children with uncontrolled asthma, the children or parents were more likely to rate the asthma as "mild."

Many asthmatic children seen in their pediatrician's office have uncontrolled asthma. This includes more than half of those with respiratory symptoms and one-third of those with other complaints. Assessment of disease control at every visit might help to improve the outcomes of childhood asthma.

COMMENT: *What do we really know about the current prevalence of uncontrolled asthma among those with a known diagnosis, in the general pediatric population? This research sheds important light on one of the great "unknowns." The most surprising result of this careful study was the extent of uncontrolled asthma found when the reason for the office visit was not primarily a respiratory one.*

Whether pediatricians would be able to screen all children with asthma at each visit, using an asthma control test, is unclear--although it would certainly be ideal. These findings suggest that all U.S. children with current asthma would benefit from at least one baseline evaluation by a specialist--regardless of parental or physician perception of severity and control--with the option for future follow-up if indicated.
K.R.M.
Liu AH, Gilsenan AW, Stanford RH, et al: Status of asthma control in pediatric primary care: results from the Pediatric Asthma Control Characteristics and Prevalence Survey Study.
Pediatrics. 2010;157:1572-1576 ♦♦

Flu Virus Is Underestimated In Asthma Exacerbations

RESPIRATORY viruses are frequently isolated in childhood asthma exacerbations. The contribution of influenza viruses is unknown. This study evaluated the burden of influenza virus in children with asthma exacerbations.

The prospective study included 339 children seen in a Paris emergency department for acute wheezing during the winter months of 2005 to 2009. Of these, 232 were hospitalized and 107 were discharged home. Virologic studies of nasopharyngeal aspirates from the hospitalized children identified bocavirus in 11.6% of cases, respiratory syncytial virus in 13.5%, and influenza A virus in 2.6%.

Of the ambulatory children, bocavirus was found in 13.0%, respiratory syncytial virus in 17.7%, and influenza A virus in 14.1%. Human metapneumovirus was detected in 8.2% of hospitalized children and 3.5% of ambulatory children.

Among children with asthma exacerbations, influenza A virus is more often detected in outpatients than in inpatients. Other viruses are found in similar proportions of children. Performing virologic studies only in hospitalized cases of childhood asthma may underestimate the contribution of influenza virus to asthma exacerbations.

COMMENT: *Many more outpatients than inpatients are being seen with influenza-triggered asthma in France, yielding a statistical skewing toward other viruses recovered from inpatients during winter months. The authors are not necessarily implying that one would underestimate the overall impact of the flu. Yes, the usual suspects (RSV and bocavirus) were also noted as important viral triggers in hospitalized patients. Unfortunately, rhinovirus was not included in this particular study.*
K.R.M.
Mandelcwajg A, Moulin F, Menager C, et al: Underestimation of influenza viral infection in childhood asthma exacerbations.
J Pediatr. 2010;157:505-506. ♦♦

Could EBC ATP Be Used for Asthma Monitoring?

BECAUSE purigenic signaling plays a pathogenetic role in asthma, adenosine and adenosine triphosphate (ATP) could be involved in airway inflammation. The ability to measure ATP in exhaled breath condensate (EBC) suggests a possible use of ATP in asthma monitoring. Measurement of ATP in EBC was evaluated as a possible asthma monitoring test.

Samples of EBC were collected from 45 adult patients with persistent asthma and 32 healthy controls. A lucerin-luciferase assay was used to measure EBC ATP, which was compared with other asthma monitoring approaches: exhaled nitric oxide, lung function tests, and the Asthma Control Test (ACT). Dilution estimated from the conductivity of vacuum-treated EBC samples was used to calculate airway ATP concentrations.

There was no significant difference between asthma patients and controls in terms of EBC ATP or calculated airway ATP levels. Nor was there any difference in EBC ATP values for asthma patients by disease control or inhaled corticosteroid use. The EBC ATP was unrelated to exhaled NO or ACT, which were significantly associated with each other. Airway droplet dilution affected the EBC ATP concentration; the calculated airway ATP level was related to FEV_1.

Measurement of EBC ATP does not appear to be useful for asthma monitoring. The findings do raise the possibility that airway ATP could be part of a general mechanism regulating airway caliber.

COMMENT: *The search for a biomarker for asthma control or risk is elusive. Exhaled breath ATP does not fit the bill, according to this study. However, the authors note that EBC collection standardization and an understanding of droplet formation are essential to evaluate findings in future studies of EBC.*
S.F.W.
Lázár Z, Cervenak L, Orosz M, et al: Adenosine triphosphate concentration of exhaled breath condensate in asthma.
Chest. 2010;138:536-542. ♦♦

Obesity Linked to Atopy in Adults

OBESITY is suspected of being a risk factor for allergic disease, although previous studies of the relationship between obesity and atopic sensitization have been inconsistent. A population-based study was performed to examine the association between obesity and sensitization in adults.

The researchers measured body mass index (BMI) and waist circumference in 1,997 adult residents of a Canadian town. Allergy assessment included skin prick testing for sensitization to house dust mite, grasses, cat, and *Alternaria*.

Overall, 35.3% of the study participants were obese and 29.7% had at least one positive skin test result. Obese subjects were more likely to have atopic sensitization: the rate was 33.3% for those with a BMI of 30 or higher, compared to 28.2% at a BMI between 25 and 30 and 27.3 at a BMI less than 25. On adjusted analysis, the odds ratio (OR) for atopy among obese subjects was 1.51. Obesity was more strongly related to atopy in women: OR 1.63, compared to 1.27 (nonsignificant) in men. In both sexes, waist circumference was significantly associated with atopy.

Obesity is significantly associated with sensitization to common allergens in adults. The results support the suggested link between adiposity and a Th2 immune response.

COMMENT: *Obesity is a major health problem associated with increased mortality. Studies of obesity and atopic sensitization have not been consistent in children and adults. These authors hypothesized that obesity might increase the likelihood of a Th2 immune response and that adipokines and cytokines secreted by white adipose tissue might result in decreased immunologic tolerance. This study of adults living in a rural community shows a significant association between obesity and atopy. The prevalence of atopic sensitization was significantly associated with obesity, including abdominal obesity. The mechanisms for the association between atopic sensitization and obesity need to be explored.*
M. F.
Chen Y, Rennie D, Cormier Y, et al: Association between obesity and atopy in adults.
Int Arch Allergy Immunol. 2010;153:372-377. ♦♦

Study Shows Safety of Ultra-Rush SLIT for Mite Allergy

SUBLINGUAL immunotherapy (SLIT) is becoming established as an alternative to subcutaneous immunotherapy. Shorter, ultra-rush regimens could help to make this approach more acceptable. This study evaluated an ultra-rush SLIT regimen for patients with allergic rhinitis due to house dust mite.

The prospective, open-label trial included 218 children and adults with allergic rhinitis, with or without asthma, caused by allergy to *Dermatophagoides*. All patients received an ultra-rush swallow SLIT regimen, with the induction phase completed within a few hours, in the hospital and under strict monitoring by an allergist. Adverse reactions were monitored, and spirometric testing was performed after each dose.

There were 32 adverse reactions. Five patients had mild local adverse reactions, including 7 local gastrointestinal reactions. The remaining 17 were local reactions: labial or mouth itching and burning. There were 8 systemic reactions, most commonly rhinitis. There were no serious or life-threatening events, and few adverse reactions after 2 weeks' follow-up.

This experience supports the safety of a high-dose SLIT regimen using *Dermatophagoides* allergen extracts. Further studies of efficacy and clinical benefit from ultra-rush SLIT protocols for perennial allergens are needed.

COMMENT: *Sublingual immunotherapy is frequently used in Europe, mostly with single allergens.* ➤➤

Several studies are being performed in the United States. This Spanish study evaluated an ultra-rush SLIT protocol in patients with dust mite allergy. All adverse reactions were mild or moderate, with no anaphylactic reactions or other serious events. The authors believe that their ultra-rush SLIT regimen is safe, but its usefulness and benefit for perennial allergens must be evaluated.
M.F.
Roger A, Justicia JL, Navarro LA, et al: Observational study of the safety of an ultra-rush sublingual immunotherapy regimen to treat rhinitis due to house dust mites.
Int Arch Allergy Immunol. 2011;154:69-75. ♦♦

CLINICAL TIDBITS

Once- vs Twice-Daily Budesonide/Formoterol in Children

IN adults with asthma, once-daily dosing with a budesonide/formoterol combination provides effectiveness similar to that of twice-daily dosing at the same dose levels. This randomized trial compared once- vs twice-daily dosing with budesonide/formoterol in asthmatic children.

The study included 521 patients, aged 6 to 15, with mild to moderate persistent asthma. After a run-in period on twice-daily budesonide/formoterol (160/18 µg/d) via pressurized metered-dose inhaler, the children were randomly assigned to twice-daily or once-daily budesonide/formoterol at the same daily dose levels; or to once-daily budesonide (160 µg/d) alone.

Compared to budesonide alone, once- or twice-daily budesonide/formoterol provided greater evening peak expiratory flow. Twice-daily budesonide/formoterol was associated with improvement in evening predose FEV_1, compared to once-daily dosing. Asthma symptoms, nighttime awakenings, and health-related quality of life were not significantly different between groups. Asthma worsening occurred in 8.2% of patients with twice-daily budesonide/formoterol vs 19.6% with once-daily treatment and 15.5% with once-daily budesonide.

In asthmatic children, twice-daily budesonide/formoterol is generally more effective than once-daily dosing. Both dosing regimens appear safe and well-tolerated, and are superior to once-daily budesonide alone.

COMMENT: *It is certainly reassuring that there were no observed safety concerns with a higher daily dose of formoterol in this study of children with asthma. But how many of us are going to recommend a medication change that yields a minor, albeit statistically significant improvement, in pulmonary function, when it requires the therapy be given twice daily vs once daily? Add the real-world challenges of suboptimal compliance with maintenance therapy, lack of parental medication supervision, and escalating co-pays to this scenario, and those few percentage points of improvement might not provide sufficient persuasion.*
K.R.M.
Eid NS, Noonan MJ, Chipps B, et al: Once- vs twice-daily budesonide/formoterol in 6- to 15-year-old patients with stable asthma.
Pediatrics. 2010;126:e565-e575. ♦♦

Aerobic Exercise Has Benefits for Asthma Patients

AEROBIC exercise programs improve fitness and reduce dyspnea in patients with asthma. Effects on asthma-related symptoms and psychologic distress were evaluated in a randomized trial of aerobic training.

The study included 101 patients with moderate or severe persistent asthma. One group received a twice-weekly, 30-minute aerobic training program. All patients received an educational program plus breathing exercises.

After 3 months, patients in the aerobic training group had significant improvement in health-related quality of life, including physical limitations, symptom frequency, and the psychosocial domain. Aerobic training was associated with increased symptom-free days and decreased anxiety and depression. As aerobic capacity increased, so did symptom-free days.

Aerobic training improves quality of life, symptoms, and mood in patients with persistent asthma. Aerobic exercise may be especially helpful for asthma patients with high psychologic distress.

COMMENT: *Exercise is good, and not just for non-asthmatics. This study demonstrates improved quality of life, including symptoms and physical domains, and decreased depression after a 3-month period of only twice-weekly aerobic exercise in patients with asthma. Interestingly, BMI was normal in both control and exercise groups. Lung function did not change nor was any attempt made to decrease controller medications.*
S.F.W.
Mendes FAR, Gonçalves RC, Nunes MPT, et al: Effects of aerobic training on psychosocial morbidity and symptoms in patients with asthma: a randomized clinical trial.
Chest. 2010;138:331-337. ♦♦

PPIs Linked to Adverse Cardiovascular Events--Even Without Clopidogrel

PATIENTS receiving antiplatelet therapy with clopidogrel and aspirin commonly take a proton-pump inhibitor (PPI) to reduce the risk of gastrointestinal bleeding. Recent studies have raised concerns of a possible increase in adverse cardiovascular events in patients taking clopidogrel plus a PPI.

This study used Danish registry data to assess cardiovascular events after hospital discharge in 56,406 patients with first-time myocardial infarction. Overall, 16.2% of patients were rehospitalized for myocardial infarction or stroke or died of cardiovascular causes. At 30 days after discharge, the hazard ratio for this composite outcome was 1.29 in patients taking a PPI--; whether or not they were also taking clopidogrel. There was no significant interaction between the use of PPI or clopidogrel.

After myocardial infarction, patients taking a PPI appear to be at increased risk of adverse cardiovascular events, whether or not they are taking clopidogrel. ➤➤

The authors believe this association reflects unmeasured confounding factors, and that the data refute concerns about risks associated with concomitant PPI and clopidogrel therapy.

COMMENT: *Epidemiologic studies may not provide definitive data but there are increasing concerns with the long-term use of PPIs, as previously discussed in* AllergyWatch. *This latest addition to the literature suggests that PPIs do not decrease the function of clopidogrel as much as they increase cardiovascular risk. So this will need to be added to potential PPI side effects, which include rebound hyperacidity, increased bacterial colonization of the stomach, and decreased absorption of vitamin B12, calcium, and iron. Allergists/immunologists need to be aware, since we commonly prescribe these agents.*
D.K.L.

Charlot M, Ahlehoff O, Norgaard ML, et al: Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study.
Ann Intern Med. 2010;153:378-396. ♦♦

REVIEWS OF NOTE

COMMENT: *This is a very readable review that could be useful when responding to the questions of pregnant patients. One response is, "If you can't breathe, you cannot have a baby, and most of the drugs are safe." However, the devil is in the details.*
D.K.L.

Louik C, Schatz M, Hernández-Diaz S, et al: Asthma in pregnancy and its pharmacologic treatment.
Ann Allergy Asthma Immunol. 2010;105:110-117. ♦♦

COMMENT: *This review provides a summary of the background to facilitate interpretation of a growing literature concerning the potential relationship between vitamin D and allergic disease and asthma.*
D.K.L.

Sandhu MS, Casale TB: The role of vitamin D in asthma.
Ann Allergy Asthma Immunol 2010;105:191-199. ♦♦

COMMENT: *This excellent review presents current knowledge about the association between infection and exacerbations of established asthma, including the mechanisms and treatment strategies.*
B.E.C.

Xepapadaki P, Papadopoulos NG: Childhood asthma and infection: virus-induced exacerbations as determinants and modifiers.
Eur Respir J. 2010;36:438-445. ♦♦

COMMENT: *With full-time emergency room doctors and hospitalists in most hospitals, allergists don't often treat their own asthma patients in the ER. But we should never lose those skills. This review article covers the state-of-the-art in emergency treatment of asthma. Some changes in recent decades are the disappearance of theophylline from the ER, the inadvisability of antibiotics for most cases, the routine inclusion of inhaled anticholinergics, and the overdue emphasis on post-ER care. Included in the article are the controversial uses of heliox, intravenous or nebulized magnesium sulfate, and intravenous leukotriene antagonists.*
R.J.M.

Lazarus SC: Emergency treatment of asthma.
N Engl J Med. 363:755-764, 2010. ♦♦

COMMENT: *Researchers have long attempted to identify THE asthma gene--but it's likely that asthma is genetically heterogeneous, just as it is phenotypically heterogeneous. This European group studied the genomes of over 10,000 asthmatics, and identified five sites on five different chromosomes that are associated with asthma in either a positive or negative way--ie, either pro-inflammatory or anti-inflammatory in asthmatics. They also confirmed previous data on one site that is strongly associated with childhood-onset asthma. Surprisingly, they found no association between the genetic determinants of IgE production and the asthma-related loci. They doubt that these findings will be useful as predictors of asthma risk in individuals.*
R.J.M.

Moffatt MF, Gut IG, Demenais F, et al: A large-scale, consortium-based genomewide association study of asthma.
N Engl J Med. 2010;363:1211-1221. ♦♦

COMMENT: *Molecular diagnosis is here to stay. This is an excellent review of recent advances in molecular strategies for diagnosing allergic disease, including microarrays.*
S.A.T.

Sastre J: Molecular diagnosis in allergy.
Clin Exp Allergy. 2010;40:1442-1460. ♦♦

COMMENT: *This current review is important because it outlines recent work involving new techniques for teasing out the relationship between asthma exacerbations and viral infections. In particular, the role of atopy as a risk or comorbid factor is discussed.*
S.A.T.

Busse WW, Lemanske RF Jr, Gern JE: Role of viral respiratory infections in asthma and asthma exacerbations.
Lancet 2010;376:826-834. ♦♦