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AllergyWatch®

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

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E-Cigarettes: Hot Puffs of Carcinogens?

As e-cigarettes continue to increase in popularity, concerns about the potential health effects increase as well. This study assessed the release of formaldehyde-releasing hemiacetals caused by heating of e-cigarette solutions.

The researchers used a "tank system" e-cigarette to vaporize commercial e-cigarette solutions. The aerosolized liquid was studied using nuclear magnetic resonance spectroscopy to assess the presence of hemiacetals.

No formaldehyde-releasing agents were detected at low voltage of 3.3 V. However, at high voltage of 5.5 V, a mean of 380 µg of formaldehyde per 10-puff sample was detected. At this rate, the researchers estimated that an e-cigarette user "vaping" 3 mL of solution per day would inhale 14.4 mg/d of formaldehyde. By contrast, the formaldehyde exposure from smoking one pack of cigarettes has been estimated at 3 mg.

The experiment raises concerns about potential exposure to high levels of formaldehyde from e-cigarette use. Depending on the calculation method used, the lifetime cancer risk associated with long-term e-cigarette use could be 5 to 15 times higher than that associated with long-term cigarette smoking.

COMMENT: *E-cigarettes are widely believed to be "safer" than traditional cigarettes. E-cigarette liquids typically have solutions of propylene glycol, glycerol (or both), plus nicotine and flavorant chemicals. This eye-opening study reports that formaldehyde-containing hemiacetals can be formed during the e-cigarette "vaping" process. The behavior of formaldehyde-releasing agents in the respiratory tract is unknown. However, if it is assumed that inhaling these agents* ➤➤

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2015 Editor-in-Chief Disclosure:
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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
- Journal of Asthama
- 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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carries the same risk as inhaling gaseous formaldehyde (a group 1 carcinogen), then long-term vaping can be associated with an incremental lifetime cancer risk 5 to 15 times higher than long-term smoking. While there are some encouraging data—such as lower levels of other known toxic chemicals in e-cigarettes—it is clear that in-depth scrutiny of the ever-changing constituents of electronic nicotine delivery devices and their impact on health is urgently warranted.

C.D.

Jensen RP, Luo W, Pankow JF, et al: Hidden formaldehyde in e-cigarette aerosols.

N Engl J Med. 2015;372:392-394. ♦♦

Refining 'On Demand' Therapy for Asthma

CURRENT guidelines for moderate persistent asthma call for regular combination therapy with an inhaled corticosteroid and long-acting β-agonist (ICS/LABA), plus rapid-acting bronchodilators as needed. Previous studies have reported that symptom-based combination treatment can be an effective alternative for patients with mild or intermittent asthma. This randomized trial compared regular ICS/LABA therapy with symptom-driven treatment for moderate asthma.

The noninferiority trial included 866 adults with stable, moderate persistent asthma. All completed a 6-week run-in period on regular inhaled budesonide and formoterol plus as-needed terbutaline. They were then assigned to receive 1 year of treatment with twice-daily placebo plus as-needed budesonide and formoterol (160/4.5 μg) or twice-daily budesonide and formoterol plus as-needed terbutaline (500 mg).

At 1 year, the percentage of patients with no treatment failure was 53.6% for as-needed treatment versus 64.0% for regular treatment. The difference of 10.3% exceeded the specified noninferiority limit of 9%. Time to treatment failure in 25% of patients was 11.86 weeks with as-needed treatment versus 28.00 weeks with regular treatment. The difference in treatment failures largely reflected more nocturnal awakenings in the as-needed group. The treatments had similar tolerability.

As-needed ICS/LABA is not as effective as regular combination therapy for moderate stable asthma. The authors note that the difference is small, suggesting that as-needed treatment could be discussed as an alternative for some patients at lower risk of treatment failure. However, the results support current recommendations for regular ICS/LABA therapy for moderate asthma.

COMMENT: *In their prior study (N Engl J Med. 2007;356:2040-2052), Papi and colleagues demonstrated efficacy of the "on demand" approach of using no daily therapy and relying solely on as-needed combination ICS/SABA in patients with mild asthma. Here they explore the utility of this approach in moderate asthmatics, demonstrating its inferiority to daily combination ICS/LABA therapy. As pointed out by Kerstjens and van den Berge in the accompanying editorial (Lancet Respir Med. 2015;3:88-89), on demand therapy appears quite attractive from a patient's perspective. However, in light of the new study, clinicians should reinforce guideline recommendations of regular use controller therapy in patients with moderate asthma.*

J.J.O.

Papi A, Marku B, Scichilone N, et al: Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial.

Lancet Respir Med. 2015;3:109-119. ♦♦

Could Hand Dishwashing Reduce Allergy Risk?

THE hygiene hypothesis suggests that lifestyle factors affecting microbial exposure during early life might affect allergy development in children. This study compared childhood allergy prevalence in families who washed dishes by hand versus those who used a dishwashing machine.

The study included 1,029 Swedish children, aged 7 to 8 years. Parents completed questionnaires regarding childhood asthma, eczema, and rhinoconjunctivitis. They were also asked whether they usually washed dishes by hand or using a dishwasher. The study also included questions of dietary factors, including fermented foods, food from farms, home cooking, and breast-feeding.

Most of the children had attended day care, about one-third had pets, and few were exposed to tobacco smoke. Eczema was reported for 23% of children in homes that used hand dishwashing versus 38% with machine dishwashing. Rates of childhood asthma were 1.7% and 7.3%, respectively. Eating fermented foods and foods bought directly from farms were associated with a lower total allergy risk.

The reduction in allergic disease with hand dishwashing remained significant on multivariate analysis: odds ratio 0.57. Allergic disease prevalence was 46% for families that used machine dishwashing, did not eat fermented foods, and did not buy food directly from farms, compared to 19% for those with two or three protective factors.

Hand dishwashing may be associated with a lower prevalence of childhood allergy compared to machine dishwashing. Certain dietary factors may "further potentiate" this protective effect. The authors discuss the findings in context of other common lifestyle factors that may affect allergy development in children.

COMMENT: *The question of whether lifestyle factors such as dishwashing methods may alter allergy prevalence was explored in a study on the practical implications of the hygiene hypothesis. The researchers found that hand dishwashing was associated with a reduced risk of development of allergic disease, compared to machine dishwashing. The risk was further reduced in a dose-response pattern if the children ate fermented food or food directly from farms. It is tempting to speculate that a less-efficient dishwashing method may enhance microbial exposure and induce tolerance. However, it is prudent to keep in mind that this is a questionnaire-based observational study, and the association is not necessarily causal. For example, atopic families with sensitive skin may be more likely to use a dishwashing machine. Nevertheless, this study raises interesting questions about our everyday habits and how they might impact immune tolerance. (Also see the editorial by Cheng and Cabana:*
Pediatrics. 2015;135:e707-708.)
C.D.

Hesselmar B, Hicke-Roberts A, Wennergren G: Allergy in children in hand versus machine dishwashing. **Pediatrics**. 2015;135:e590-e597. ♦♦

FOCUS ON PROBIOTICS

Clinical Benefits of Lactobacillus in Childhood AD

THERE is growing interest in the possibility that probiotics may be a useful treatment for atopic dermatitis (AD). Further study is needed to document strain-specific clinical benefits. Two *Lactobacillus* species were studied for their effects on disease severity and other outcomes in children with AD.

The randomized trial included 220 children, aged 1 to 18 years, with moderate to severe AD. Patients were assigned to probiotic therapy with *Lactobacillus paracasei, Lactobacillus fermentum*, or a combination of the two. Controls received placebo; treatments continued for 3 months. Outcome measures included AD severity scoring with SCORAD, the Family Dermatology Life Quality Index (FDLQI), and the Children's Dermatology Life Quality Index (CDLQI). Skin prick tests, IgE and cytokine levels, and urine biomarkers were assessed as well.

From baseline means of 50 to 54, SCORAD scores decreased to between 24 and 28 in the probiotic groups at 3 months, compared to about 39 in the placebo group. The reduction in disease severity remained significant even 4 months after probiotic treatment was stopped. All three probiotic treatments were also associated with reductions in FDLQI and CDLQI scores and IgE levels.

The probiotic groups also had decreases in tumor necrosis factor-α, urine eosinophilic protein X, and the oxidative stress biomarker 8-hydroxydeoxyguanosine, along with increases in interferon-γ and transforming growth factor-β. However, the only significant difference was a decrease in interleukin-4. In subgroup analyses, reductions in SCORAD were greater for children younger than 12 years, those breast-fed for longer than 6 months, and those sensitized to house dust mite.

Treatment with *L. paracasei, L. fermentum*, or both is associated with significant and lasting reduction in AD severity in children. The authors call for longer-term follow-up studies to examine the maintenance of the therapeutic and oxidative effects.

COMMENT: *Previous studies have demonstrated positive results in preventing the development of eczema with probiotics (Rautava et al: J Allergy Clin Immunol. 2012;130:1355-1360). Likewise, small-scale studies using* Lactobacillus *have demonstrated improvement in atopic dermatitis symptoms (Weston et al: Arch Dis Child 2005;90:892-897). The study by Wang and Wang extends our understanding by demonstrating a significant improvement in SCORAD, as well as quality of life measures. Interestingly, the SCORAD remained improved even 4 months after discontinuing the probiotic. Subgroup analysis found that the greatest improvement in children younger than 12. The authors postulate that this difference in efficacy may be a consequence of the fact that the intestinal microbiota is less amenable to change in older children. This is one more study suggesting the microbiome's importance in allergy.*
J.J.O. ►►

Wang I-J, Wang J-Y: Children with atopic dermatitis show clinical improvement after Lactobacillus exposure. **Clin Exp Allergy**. 2015;54:779-787. ♦♦

High Response to Combined Probiotic/OIT Approach for Peanut Allergy

RECENT studies have reported successful desensitization with oral immunotherapy (OIT) for egg, milk, and peanut allergy, although the ability to induce sustained tolerance remains unclear. An approach using a bacterial adjuvant combined with OIT has been proposed as a potentially useful treatment for food allergy. This study reports a combined probiotic/OIT approach for peanut allergy.

The randomized, double-blind trial included 62 children with peanut allergy, aged 1 to 10 years. After stratification by age and wheal size on peanut skin testing, one group of children received probiotic and peanut oral immunotherapy (PPOIT), consisting of *Lactobacillus rhamnosus* CGMCC 1.3724 plus a peanut OIT protocol. Controls received placebo. The main outcome of interest was sustained unresponsiveness to oral peanut for 2 to 5 weeks after cessation of treatment.

Fifty-six patients completed the 18-month study. The study definition of "possible sustained unresponsiveness" was met by 82.1% of children in the PPOIT group compared to 3.6% in the placebo group. The number needed to treat was 1.27 to achieve sustained unresponsiveness in one additional child.

Desensitization was achieved in 89.7% of children assigned to PPOIT versus 7.1% in the placebo group. Treated children also had reduced skin prick test responses to peanut, lower peanut-specific IgE levels, and higher peanut-specific IgG_4 levels. Adverse events were more common in the PPOIT group, mainly related to maintenance dosing at home.

This randomized trial shows a high rate of "possible sustained unresponsiveness" in peanut-allergic children treated with a combined probiotic/OIT approach. The study also provides evidence of alterations in peanut-specific immune responses. More research is needed to confirm sustained responsiveness and clarify the relative roles of probiotics versus OIT.

COMMENT: *Oral immunotherapy for food allergy has been shown to induce desensitization. However, it is unclear whether this results in true tolerance, with ability to eat the food even after the OIT is stopped. A novel approach combining peanut protein with a probiotic for OIT resulted in impressive immune changes in skin prick tests, specific IgE levels, and sIgG4 levels. Even more remarkable, 82% of treated children were able to tolerate peanut protein 2 to 5 weeks after PPOIT was stopped, compared to just 3.6% of those receiving placebo. The authors suggest that future food allergy immunotherapy trials should use new terminology such as "4-week sustained unresponsiveness" to more clearly define the precise period of secondary avoidance.*
S.M.F.

Tang MLK, Ponsonby A-L, Orsini F, et al: Administration of a probiotic with peanut oral immunotherapy: a randomized trial. **J Allergy Clin Immunol**. 2015;135:737-744. ♦♦

Bring on the Sun!

VITAMIN D deficiency in patients with chronic obstructive pulmonary disease (COPD) can predispose to upper respiratory infections, which are an important cause of exacerbations. This randomized trial evaluated the effects of vitamin D_3 supplementation on COPD exacerbations and upper respiratory infections in patients with COPD.

In the multicenter UK trial, 240 patients with COPD were assigned to receive vitamin D_3 supplementation, six oral doses of 3 mg over 1 year, or placebo. Overall, there was no significant difference between groups in time to first moderate or severe COPD exacerbation or time to first upper respiratory infection.

In a prespecified subgroup analysis, vitamin D was associated with a significant reduction in time to first moderate or severe exacerbation among patients with a baseline serum 25-hydroxyvitamin D concentration less than 50 nmol/L. The subgroup analysis found no significant difference in risk of upper respiratory infection.

The results suggest that vitamin D supplementation can reduce exacerbation rate among COPD patients with baseline vitamin D deficiency. There is no association with the risk of upper respiratory infections. The protective effect on exacerbations might involve vitamin D-mediated suppression of proinflammatory cytokines and chemokines.

COMMENT: *We now have data that beyond asthma, there may be utility in vitamin D supplementation for COPD patients with vitamin D deficiency. In this multicenter study, subjects with baseline vitamin D levels of less than 50 nm/L who underwent supplementation with six 2-monthly oral doses of 3 mg vitamin D demonstrated a reduction in moderate or severe exacerbations of COPD. Interestingly, there was no improvement in upper respiratory infections. The vitamin D story continues.*
J.J.O.
Martineau AR, James WY, Hooper RL, et al: Vitamin D_3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. **Lancet Respir Med**. 2015;3:120-130. ♦♦

Is Oral Immunotherapy for CMA Safe in Asthma Patients?

PATIENTS with asthma and food allergies are at high risk for severe reactions to food exposures. Milk oral immunotherapy is safe and effective for most patients with cow's milk allergy (CMA), but there are limited data on the outcomes of this treatment in ➤➤

patients with asthma. The course and long-term outcomes of milk oral immunotherapy were assessed in children with versus without asthma.

In 2010-11, the researchers administered milk oral immunotherapy to 194 children aged 6 years or older with IgE-mediated CMA. Of these, 101 children had asthma. In both groups, the oral milk dose was escalated to full (greater than 7.2 g of milk protein) or partial desensitization. Outcome assessment included skin prick testing in all patients and spirometry in the asthmatic group.

At baseline, children with asthma at all severity levels had a higher rate of anaphylactic reactions, 84.2% versus 64.5%; emergency department visits, 68.3% versus 51.6%; and hospitalizations, 32.7% versus 18.3%. During both the induction and home phases of milk oral immunotherapy, asthmatic children had more reactions and required more injectable epinephrine treatment.

However, the response to milk oral immunotherapy was good, with 86.1% of asthmatic children achieving at least partial desensitization. Children with moderate to severe asthma were less likely to achieve full desensitization: 51.5% versus 68.8%. Several months after completing oral immunotherapy, most of the asthmatic children were freely consuming dairy products. Adverse reactions continued to occur, but severe reactions became less common over time.

Asthmatic children with CMA are at risk of more severe reactions to milk oral immunotherapy. However, most achieve partial desensitization likely to protect them against accidental exposure--including those with moderate to severe asthma. Especially because of their high baseline rate of anaphylaxis, asthmatic children "should not be excluded from consideration" of milk oral immunotherapy.

COMMENT: *Oral immunotherapy is a promising treatment for patients with food allergy, but many studies have excluded patients at highest risk. This study looked at groups of patients with CMA, with or without asthma. As would be expected, the patients with asthma had increased risk for severe reactions. However, most were able to consume some milk, which would likely protect the patient in case of accidental exposure. While some patients did require treatment with epinephrine, most were able to achieve desensitization and tolerate cow's milk after treatment. The results are reassuring for the long-term outcome of these patients.*
V.H.-T.

Elizur A, Goldberg MR, Levy MB, et al: Oral immunotherapy in cow's milk allergic patients: course and long-term outcome according to asthma status.
Ann Allergy Asthma Immunol. 2015;114:240-244. ♦♦

Skin Testing for Corticosteroid Allergy: History Matters

IMMEDIATE hypersensitivity reactions to corticosteroids are a known but rare problem, with a reported incidence of 0.1%. There are few data on the results of corticosteroid skin testing--the largest reported series included just 7 patients. An experience with skin testing for suspected corticosteroid hypersensitivity in 23 patients is reported.

The patients--65% female, mean age 50 years--were tested at a New Zealand hospital from 2005 to 2012. Common presentations included anaphylaxis in 8 patients, acute urticaria/rash or angioedema in 4, and delayed flushing in 3. Thirteen patients reacted to intra-articular steroid injections.

Twenty-one patients were tested with a standard panel of prednisolone, triamcinolone, methylprednisolone, hydrocortisone, and dexamethasone. The other 2 were tested using the implicated steroid only. A 10% steroid stock concentration was used for skin prick testing (SPT) and 1:1000, 1:100, and 1:10 dilutions for intradermal testing. Wheal sizes of 3 mm larger than negative controls were considered positive.

Skin test results were positive in 8 of the 23 patients, including 7 of the 8 patients with a history of anaphylaxis. Results were positive with SPT in 2 cases and intradermal testing in 6. There was 1 apparent false-positive skin test result, in a patient with a positive unblinded oral challenge.

Skin testing can be diagnostic in patients with a clear history of immediate hypersensitivity reactions to corticosteroids--particularly anaphylaxis. Testing should include both SPT and intradermal testing; because of cross-reactivity, a panel should be used. The authors note that supervised challenge is the only definitive test to prove tolerance, but was performed in few of their patients with negative skin tests.

COMMENT: *While not common, corticosteroid allergy is a real phenomenon. Whether these reactions are IgE-mediated or not has been debated in the literature. This study from New Zealand reports on the largest series of patients (n=23) undergoing skin testing, most with a protocol of five different steroids. Patients with histories of anaphylaxis had positive skin tests in 7 of 8 cases, compared to 1 out of 4 patients with urticarial reactions. Skin tests were negative in all patients with presyncope, flushing, and delayed reactions. Rare false positive and false negative tests also occurred. As in other drug reactions, skin testing to corticosteroids appears to have utility--particularly in those with histories of anaphylaxis--but is not infallible.*
D.A.K.

Baker A, Empson M, The R, Fitzharris P: Skin testing for immediate hypersensitivity to corticosteroids: a case series and literature review.
Clin Exp Allergy. 2015;45:669-676. ♦♦

Climate Factors Affect Regional Hay Fever Rates

ENVIRONMENTAL factors likely contribute to regional differences in allergic diseases, including hay fever. National children's health and climate data were used to assess the relationship between climate factors, pollen counts, and statewide variations in hay fever prevalence.

The study used information on a representative sample of nearly 92,000 children and adolescents from ➤➤

the 2007 National Survey of Children's Health, merged with 2006-07 National Climate Data Center and Weather Service data. Specific climate factors of interest were relative humidity, indoor heating degree days, precipitation, Palmer Hydrological Drought Index (PHDI), clear sky and issued ultraviolet (UV) indices, stratospheric ozone levels, outdoor air temperature, and total pollen counts. Multivariate analyses controlled for sex, race/ethnicity, age, household income, and birthplace.

Overall prevalence of pediatric hay fever was 18.0%, with the highest rates seen in the southeastern and southern states. Hay fever was more common in older children, boys, and higher-income households and lower in Hispanic and non-U.S.-born children. Prevalence was lower in states in the lower quartiles of mean annual relative humidity, PHDI, heating degree days, and stratospheric ozone levels,

In contrast, hay fever prevalence increased with mean annual temperature, pollen counts, and issued UV levels. Prevalence was also increased in the fourth quartile of mean annual precipitation. Principal component analysis identified two important combinations of correlated factors: high temperature, low heating degree days, high issued UV index, low PHDI, and high pollen counts; and high humidity, precipitation, and precipitation with minimal effects from pollen counts.

Climate has a significant impact on US regional prevalences of pediatric hay fever. Hay fever appears most common in areas with very dry, hot, and sunny climates with high pollen counts, and in those with wet and rainy conditions. Further studies should address the likely effects of climate change on childhood allergic disease.

COMMENT: *This is a report of a large data base and includes pollen counts from the National Allergy Bureau. Hay fever was more prevalent in Southern states with higher temperatures, more UV radiation, wet humid conditions, and higher pollen counts. Besides the use of the term "hay fever," the other main weakness of this study is the use of self-reporting for identifying children with allergic respiratory problems. The overall hay fever prevalence of 18% is similar to other reports using telephone surveys. Overall the results are not surprising, but they reaffirm that we as allergists should continue to monitor weather and climate since it does impact our patients.*
S.M.F.

Silverberg JI, Braunstein M, Lee-Wong M: Association between climate factors, pollen counts, and childhood hay fever prevalence in the United States.
J Allergy Clin Immunol. 2015;135:463-469. ♦♦

Is Rhinitis in the Elderly Correctly Diagnosed?

WITH rising allergy rates and an aging population, local allergic rhinitis (LAR) appears to be increasing in older adults. Previous reports suggest that LAR is underdiagnosed generally, and in older adults particularly. This study assessed the prevalence of LAR among elderly patients previously diagnosed with rhinitis.

The study included 219 older patients, aged 65 to 89 years, with rhinitis lasting longer than 12 months but no established diagnosis. Evaluation included a clinical allergy questionnaire along with skin prick tests, serum total specific IgE measurement, and nasal provocation tests using common aeroallergens. To assess nasal specific IgE levels, nasal lavage was performed at baseline and after provocation.

Twenty-one percent of these elderly patients were diagnosed with LAR, based on production of specific IgE in the nasal mucosa and a positive response to nasal provocation testing in the absence of atopy on conventional tests. About half of the remaining patients were diagnosed with allergic rhinitis. In both the LAR and allergic rhinitis groups, the most commonly implicated allergen was house dust mite: 63.0% and 56.4%, respectively. The two groups were similar in terms of nasal symptom scores and types of allergens.

Patients with clinical responses to nasal provocation had significant increases in nasal IgE. Elderly patients with a diagnosis of allergic rhinitis were more likely to be sensitized to multiple allergens, compared to those with LAR.

This study suggests that LAR may be found in about 20% of elderly patients with a nonspecific diagnosis of rhinitis, while another 40% are diagnosed with allergic rhinitis. The authors discuss the implications for diagnosis of rhinitis in older adults, including the situations where nasal IgE measurement may be indicated.

COMMENT: *Elderly patients may present for evaluation to the allergist with new-onset or even chronic symptoms of rhinitis. In this study, more than one-fifth of such patients were diagnosed with LAR--all of whom were previously misdiagnosed. The authors recommend thorough evaluation consisting of skin prick tests, serum IgE, and nasal provocation testing for elderly patients with rhinitis. Nasal lavage studies found that increased nasal IgE was present at baseline as well as 6 hours after nasal provocation, consistent with both early- and late-phase reactions. While this may not be practical for everyday practice, severely affected patients or those who do not respond to treatment, may benefit from more thorough evaluation for rhinitis.*
V.H.-T.

Bozek A, Ignasiak B, Kasperska-Zajac A, et al: Local allergic rhinitis in elderly patients.
Ann Allergy Asthma Immunol. 2015;114:199-202. ♦♦

Dust Mite and BSM Remodeling: New Targets for Therapy?

REMODELING of the bronchial smooth muscle (BSM) develops early in the course of asthma and is associated with decreased lung function. House dust mite (HDM), the most frequent asthma allergen, acts in vivo on the bronchial epithelial layer. This study looked at how HDM stimulation of the bronchial epithelial layer affects BSM remodeling in asthma.

The study used a newly developed in vitro model combining an epithelial layer in air-liquid interface ➤➤

interacting with BSM. It included bronchial specimens from 22 patients with severe asthma and 27 nonasthmatic controls. Using BrdU incorporation, the researchers showed a selective increase in BSM cell proliferation in samples from asthma patients.

Studies of epithelial cytokines and growth factors suggested that the proliferation of BSM cells occurred through protease-activated receptor-2 activation and release of leukotrienes. In both in vitro and ex vivo studies, BSM from patients with severe asthma overexpressed the leukotriene receptor CystLR1.

Exposure to HDM seems to have a selective effect on BSM remodeling via an epithelium-dependent leukotriene C4 production. The findings suggest possible therapeutic targets at both the epithelial and smooth muscle levels. The authors note that, in the study model, montelukast abolished the proliferation of asthmatic BSM cells in response to HDM stimulation of the epithelium.

COMMENT: *This analysis of house dust mite sensitivity, severe asthma, and leukotriene expression gives some important insights into the regulation of airway smooth muscle tone. This study gives reason to re-evaluate the role of anti-leukotriene drugs in the treatment of severe asthma. Also see the editorial by Boyce and Barrett (Am J Respir Crit Care Med. 2015:191;496-497).*
B.E.C.

Trian T, Allard B, Dupin I, et al: House dust mites induce proliferation of severe asthmatic smooth muscle cells via an epithelium-dependent pathway.
Am J Respir Crit Care Med. 2015 191:538-546. ♦♦

Smoking: Bad for Asthma and the Airway Lumen

SMOKING in asthma patients is associated with worse symptom control and impaired corticosteroid efficacy. Changes in the structure and function of the segmental or small airways may contribute to the smoking's effects on disease control. This CT study compared segmental airway luminal thickness and wall diameter in smoking versus nonsmoking asthma patients.

Chest CT scans were performed in 93 patients with mild, moderate, or severe asthma, including 46 smokers (median 34 pack-years) and 47 never-smokers. Wall thickness and luminal area were measured in the right bronchial and left bronchial segmental airways. Associations between the CT measures and current symptom control were assessed.

Asthmatic smokers showed significant reductions in luminal area of the fifth-generation segmental airways: RB10 16.6 versus 19.6 mm^2 and LB10 14.8 versus 19.9 mm^2. The differences were most pronounced in patients with severe asthma. Wall thickness and larger airway dimensions were not significantly different for smokers versus nonsmokers. Reduced lumen areas in RB10 or LB10 were associated with worse symptom control, reduced postbronchodilator forced midexpiratory flow rate, and a lower ratio of residual volume to total lung capacity.

Asthma patients who smoke have reduced segmental airway lumen area. The difference is most marked in severe asthma, and is linked to worse asthma control and small airway dysfunction. Further studies are needed to assess the mechanism of smoking-related segmental small airway dysfunction and to evaluate possible therapies, such as extra-fine particle inhaled corticosteroids.

COMMENT: *Computed tomography studies show that the lumen area as well as wall thickness are different in asthmatics and controls. This study from Scotland looked at the effects of smoking in asthma in relation to symptom control and CT changes. Not surprisingly, asthmatics who smoked had worse asthma control. They also had smaller airway lumen in the small airways, but no change in wall thickness, compared to nonsmoking asthma patients. Reduced small airway lumen was associated with poor asthma control in smokers but not in nonsmokers, and was more pronounced in those with severe disease. This study suggests that in addition to factors like corticosteroid insensitivity, small airway changes from smoking may contribute to worse symptom control in asthma.*
D.A.K.

Thompson NC, Chaudhari R, Spears M, et al: Poor symptom control is associated with reduced CT scan segmental airway lumen area in smokers with asthma.
Chest. 2015;147:735-744. ♦♦

Can Genetic Biomarkers Predict AERD?

PATIENTS with aspirin-exacerbated respiratory disease (AERD) often have severe, eosinophilic asthma with chronic rhinosinusitis and nasal polyps associated with hypersensitivity to aspirin and/or nonsteroidal anti-inflammatory drugs. The gene encoding dipeptidyl-peptidase 10 (DPP10) is a possible contributor to asthma susceptibity and decreased lung function. This study evaluated genetic variants of *DPP10* as susceptibility factors for AERD or severe asthma.

The case-control study included 274 Korean patients with AERD and 272 with aspirin-tolerant asthma, along with 99 healthy controls. Based on a preliminary genomewide association study, the analysis targeted the rs17048175 single-nucleotide polymorphism.

The results showed that rs17048175 TT genotype was associated with the AERD phenotype, but not with aspirin-tolerant asthma. Patients with the TT genotype were young and had higher total IgE levels; there were no significant associations with chronic rhinosinusitis or total or sputum eosinophil count. Patients with AERD had higher serum DPP10 levels, which were positively correlated with eosinophilic inflammation markers such as 15-HETE and YKL-40/CHI3L1. At a cutoff value of 7.81 ng/mL, serum DPP10 distinguished between the AERD and control groups with a sensitivity of 72.1% and specificity of 75.9%.

A specific variant of *DPP10* may be a genetic biomarker of AERD. The rs17048175 single-nucleotide polymorphism may contribute to airway eosinophilic inflammation and susceptibility to AERD. ►►

COMMENT: *Expanded use of genetic tests holds promise for determining the phenotype of patients with atopy. The study looked at whether DPP10 is an important genetic biomarker in patients with AERD susceptibility. Patients with AERD had higher levels of DPP10, compared to controls or those with aspirin-tolerant asthma. DPP10 may be involved in chronic eosinophilic inflammation and susceptibility to AERD, although probably not acute inflammation. Correlations with serum 15 HETE levels were also seen. The authors recommend further studies to investigate the role of DPP10 in the pathogenesis of AERD.*
V.H.-T.
Kim S-H, Choi H, Yoon M-G, et al: Dipeptidyl-peptidase 10 as a genetic biomarker for the aspirin-exacerbated respiratory disease phenotype.
Ann Allergy Asthma Immunol. 2015;114:208-213. ♦♦

Prednisolone for Rhinovirus-Induced Wheezing: Randomized Trial

CHILDREN with episodes of rhinovirus-induced wheezing are at risk of recurrent wheezing. Previous trials have not supported the efficacy of systemic corticosteroids for treatment of early wheezing, but no study has focused on patients whose wheezing is caused by rhinovirus. This trial evaluated the outcomes of prednisolone for treatment of children with first episodes of rhinovirus-induced wheezing.

The randomized, double-blind, placebo-controlled trial included 79 children, aged 3 to 23 months, with their first episode of wheezing. The presence of rhinovirus was confirmed by polymerase chain reaction (PCR) from a nasopharyngeal aspirate. Children in the intervention group received oral prednisolone at an initial dose of 2 mg/kg, then 2 mg/kg/d in two divided doses for 3 days. Controls received placebo. Outcomes of interest were new episodes of physician-confirmed wheezing within 2 months, the number of wheezing episodes at 12 months, and the start of regular asthma controller medications within 12 months.

Complete information was available for 74 children: mean age 13 months, 28% with atopy. At 2-week assessment, children assigned to prednisolone had less coughing, rhinitis, noisy breathing, severe breathing problems, and nighttime respiratory symptoms. However, all long-term outcomes were similar between the prednisolone and placebo groups.

On interaction analysis, the benefits of prednisolone were greatest among the 25 children with a rhinovirus load greater than 7,000 copies/mL. For this group, treatment was associated with a reduced risk of physician-confirmed recurrence at both 2 and 12 months.

Overall, prednisolone does not reduce recurrence risk in young children with their first episode of acute rhinovirus-induced wheezing. However, this benefit may appear for the subgroup of children with high rhinovirus loads, which may indicate early pulmonary inflammation.

COMMENT: *This well-designed randomized study addresses the question of the effectiveness of prednisolone for acute treatment of young children with rhinovirus-induced wheezing. The sample size was small and there was a 45-hour delay in giving the prednisolone, since it took that time to complete the rhinovirus PCR. Another limitation is that most patients were hospitalized, so it will be hard to project these results to an out patient setting. The authors suggest that prednisolone can reduce lung inflammation in children with high viral loads, but should not be routinely recommended for all children with their first rhinovirus-induced wheezing illness. Larger trials using quantitative PCR will be helpful to guide our treatment recommendations in the future.*
S.M.F.
Jartti T, Nieminen R, Vuorinen T, et al: Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode.
J Allergy Clin Immunol. 2015;135:61-68. ♦♦

When is Watchful Waiting Appropriate for Kids with Chronic Cough?

A critical step in evaluating children with chronic cough is distinguishing those with "specific cough" requiring treatment versus those whose cough is likely to resolve without treatment. Current guidelines identify "cough pointers," based on signs, symptoms, and simple tests. The ability of cough pointers to differentiate specific from nonspecific cough was evaluated in a large sample of children with chronic cough.

The analysis included data on 326 Australian children referred for evaluation of chronic cough: median duration 3 to 4 months. Guideline-recommended cough pointers were evaluated for sensitivity, specificity, and predictive value. In 40 children, the cough resolved with the "watchful waiting" approach, ie, with no specific treatment. Thus the pretest probability of specific cough was 88%.

Children with spontaneous resolution were older and more likely to have dry cough, to be non-Indigenous, and to have normal chest x-rays. Cough pointers associated with a specific diagnosis included wet cough, wheezing or reversible airway obstruction, and abnormal chest radiograph. All children with specific cough had at least one cough pointer, compared to just 2 of the 40 children with spontaneous resolution. The presence of any cough pointer had a sensitivity of 100% for specific cough, while the absence of all pointers had a negative predictive value of 100%.

In children with chronic cough, individual cough pointers identify children likely to have a specific cause of cough. In contrast, those with no cough pointers are very unlikely to have specific cough, and thus are candidates for a watchful waiting approach. The authors note that their findings in a hospital cohort of mainly young children may not apply to primary care settings and older children.

COMMENT: *Chronic cough is a common reason parents seek consultation for their children.* ➤➤

Appropriate diagnosis is key to management, but in some patients cough will resolve spontaneously. This study from Australia evaluated a hospital cohort of 326 children referred for chronic cough who underwent an evaluation based on an evidence-based cough algorithm. The researchers analyzed the predictive value of "cough pointer" findings on history, physical examination, chest x-ray, and spirometry—23 in all—in determining whether a specific cause of cough would be found or whether spontaneous resolution would occur. While all of these findings had high likelihood ratios (many that were infinite), the combination had the best negative predictive value. All children with no "cough pointers" (12% of the total group) had spontaneous resolution of their cough. For this group, watchful waiting would be appropriate. Whether these findings are generalizable is not clear, but they certainly suggest that a limited evaluation may be appropriate for a minority of children with chronic cough.
D.A.K.
Chang AB, Van Asperen PP, Glasgow N, et al: Children with chronic cough: when is watchful waiting appropriate? Development of likelihood ratios for assessing children with chronic cough.
Chest. 2015;147:745-753. ♦♦

Hygiene, Vitamin D, Dust Mites, and Asthma: New Insights

THE original hygiene hypothesis suggested that increased allergy risk might be linked to lack of infections. Over time, the idea developed that allergy risk is related to "excessive cleanliness" in affluent households. Meanwhile, there is no evidence linking allergic diseases to home or personal cleanliness. Data from a German birth cohort study were used to evaluate the association of personal hygiene and home cleanliness to asthma and allergic disease risk.

The analysis included comprehensive questionnaire data on home or personal cleanliness to allergic diseases at school age in 399 children. Bacterial markers in floor and mattress dust samples were evaluated as well.

The data suggested that higher personal cleanliness was associated with lower levels of bacterial compounds in household dust samples. However, while home cleanliness was related to decreased amounts of dust, it had no effect on microbial markers. Muramic acid exposure was associated with a lower likelihood of asthma at school age: adjusted odds ratio (OR) 0.59. Higher levels of endotoxin in mattress dust during infancy were related to lower rates of atopic sensitization and asthma at school age: OR 0.73 and 0.72, respectively. However, measures of personal and home cleanliness were unrelated to the development of childhood allergies.

Asthma and allergies in school-age children are related to markers of bacterial exposure in house dust. Although personal and home cleanliness affect dust parameters, they do not influence allergic disease outcomes. The results suggest a protective effect of "definite yet unknown microbial exposures," which are not reflected by the nonspecific bacterial markers used in this study.

COMMENT: *In this study, personal hygiene does not seem to be related to increased incidence of allergy and asthma. The accompanying editorial by Weiss and Litonjua (Am J Respir Crit Care Med. 2015;191:492-493) extends these observations to include the link between alterations in the gut microbiome and vitamin D deficiency. These factors interact with immunologic stimulants such as house dust mite and endotoxins. The discussion may give significant insight into the genesis of allergic and autoimmune diseases.*
B.E.C.
Weber J, Illi S, Nowak D, Schierl R, et al: Asthma and the hygiene hypothesis: does cleanliness matter?
Am J Respir Crit Care Med. 2015;191:522-529. ♦♦

Cephalosporin Skin Tests: Helpful if Positive, but Beware False Negatives

CEFUROXIME, a second-generation cephalosporin, is commonly implicated in perioperative hypersensitivity reactions to intravenous antibiotics. The diagnostic performance of various tests for cefuroxime allergy has not been established. The authors report their anesthesia allergy center's experience with diagnosis of perioperative cefuroxime hypersensitivity.

The analysis included 89 patients referred for evaluation of perioperative hypersensitivity reactions who had been exposed to cefuroxime. The test protocol included skin tests, in vitro tests, and titrated intravenous provocation.

Based on at least two positive tests and/or a positive provocation, 23 patients were considered cefuroxime positive, representing 25.8% of patients exposed to this drug. Skin test results were positive in 13 patients, specific IgE and histamine release tests in 4 patients each, and provocation tests in 14 patients. Eight patients were positive on provocation testing only--a rate of 34.8%. On assessment of time to the index reaction after cefuroxime exposure, 22 of 22 positive patients reacted within less than 15 minutes. However, reaction occurred within the same time frame in 65.5% of patients who tested negative for cefuroxime hypersensitivity.

Cefuroxime is an important cause of perioperative drug hypersensitivity. A combination of several skin tests is recommended to increase the sensitivity of testing for cefuroxime hypersensitivity. However, more than one-third of patients who react to cefuroxime have negative results on all tests besides intravenous provocation.

COMMENT: *Numerous studies of cephalosporin skin testing have been published, but this study from Denmark of cefuroxime testing in perioperative anaphylaxis sheds some new light. As in other recent studies, cefuroxime was one of the most common causes of perioperative anaphylaxis, accounting for 25% of cases where it was used. Interestingly, skin prick tests were frequently positive with a sensitivity of 56%--higher than intradermal testing--although this may have been due to a lower than typical intradermal testing concentration. Boldly, the authors also challenged 7 patients with positive skin prick tests and 100% reacted!* ➤➤

It's important to note that 34% of patients had negative skin tests and in vitro tests, yet reacted to drug provocation. Whether a more concentrated intradermal test would have picked these up is unknown. The authors suggest drug provocation should be performed when tests are negative, even in perioperative anaphylaxis. While that's a logical conclusion, this approach certainly confers significant risk.
D.A.K.
Christansen IS, Kroigaard M, Mosbech H, et al: Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime.
Clin Exp Allergy. 2015;45:807-814. ♦♦

Cockroach Extracts May Be Degraded in Allergen Mixtures

FOR *Alternaria* and German cockroach allergens, degradation by endogenous proteases can occur in combination with other insect and fungal extracts. Few studies have looked at the compatibility of other high-protease products in similar immunotherapy combinations.

This study examined the stability and compatibility of *Aspergillus fumigatus* and American cockroach allergens when mixed with other high-protease fungal and insect extracts, at levels similar to those used for subcutaneous immunotherapy. The mixtures were evaluated using enzyme-linked immunosorbent assays and immunoblotting. Samples at 10% to 50% glycerin concentrations were assessed after up to a year of refrigeration.

In control samples and mixtures, *Aspergillus* extract showed moderate to high activity under all study conditions. However, American cockroach extract was partly degraded at glycerin concentrations of 10% to 25%. Cockroach extract also showed decreased compatibility in combination with fungal extracts at a 25% glycerin concentration. At 25% to 50% glycerin, American cockroach allergen was stable in combination with other insect extracts.

Added to previous studies, the results suggest cockroach allergens may be degraded by proteases in fungal extracts. Separate formulation of high-protease functional and insect extracts may provide more consistent allergen delivery throughout the course of subcutaneous immunotherapy.

COMMENT: *These authors demonstrate that* Aspergillus *extracts had favorable stability after mixing with high-protease products. However, American cockroach extracts were unstable in less than 50% glycerin, even without protease-containing allergens. Mixtures with high glycerin concentrations may be needed to produce compatible patient formulations for allergen immunotherapy.*
C.C.R.
Grier TJ, Hall DM, Duncan EA, Coyne, TC: Mixing compatibilities of Aspergillus and American cockroach allergens with other high-protease fungal and insect extracts.
Ann Allergy Asthma Immunol. 2015;114:327-334. ♦♦

Statewide Asthma Repository--Framework for Comparative Effectiveness Trials

ASTHMA varies in terms of phenotype and natural history; current treatments fail to achieve disease control in 40% to 70% of patients. The authors report the development and initial findings of a "comprehensive repository" of data on childhood asthma and outcomes—including variations in clinical practice—in Ohio children's hospitals.

The statewide Ohio Pediatric Asthma Repository included children, aged 2 to 17, seen at six participating children's hospitals for asthma exacerbations or reactive airway disease. The researchers analyzed data on 1,012 children enrolled over a 10-month period, including medical, social, and environmental histories.

The six hospitals varied substantially in population served, clinical care for emergency department and admitted patients, ICU use, discharge criteria, and length of stay. Percentages of patients on public insurance were highest in Cleveland (72%) and Cincinnati (65%). Emergency department use of intravenous magnesium sulfate was highest in Cincinnati (37%) and Akron (33%), while intramuscular epinephrine was most frequently used in Columbus (15%).

Rates of ICU admission were highest in Cleveland (44%) and Columbus (41%), which also had the highest proportions of long-stay patients (95% and 85%, respectively). Discharge prescription of inhaled corticosteroids was more likely for children with moderate/severe asthma (odds ratio 2.7) but was unrelated to length of stay. Asthma severity and/or risk were also unrelated to length of stay.

These statewide data on inpatient pediatric asthma show variability in clinical practices across Ohio children's hospitals. Future reports will seek to define the practices leading to best clinical outcomes across hospitals, and whether personalized or phenotype-targeted strategies lead to improved outcomes.

COMMENT: *This study describes a unique and ingenious approach to identifying the practices and phenotypes associated with the best health outcomes in a region. The Ohio Pediatric Asthma Repository links clinical, environmental, and biologic data for inpatient pediatric asthma across six Ohio children's hospitals, with the ultimate goal of ensuring implementation of best practices across these centers. It is interesting to note the variability across these leading pediatric centers, ranging from differences in the population served to care practices. This degree of courageous transparency and honest in-depth analysis is not only refreshing, but also a harbinger of how data needs to be collected and compared in the future. Such approaches will enable conduct of comparative effectiveness studies essential to developing clinical pathways tailored to asthma phenotypes, and ensure standardization and optimization of healthcare outcomes.*
C.D.
Biagini Myers JM, Simmons JM, Kercsmar CM, et al: Heterogeneity in asthma care in a statewide collaborative: the Ohio Pediatric Asthma Repository.
Pediatrics. 2015;135:271-279. ♦♦

Audiovisual Reminders Improve ICS Adherence

LOW adherence to prescribed asthma medications is a major source of preventable morbidity and mortality. Previous studies of inhalers with electronic reminder devices have shown improvements in adherence, but not in asthma clinical outcomes. This study evaluated an inhaler with an audiovisual reminder function for effects on adherence and outcomes in children at risk of asthma exacerbations.

The randomized trial included 220 school-aged children with a prescription for regular inhaled corticosteroids (ICS) who had a recent emergency department (ED) visit for asthma exacerbation. All children received the SmartTrack electronic monitoring device, with or without activation of the audiovisual reminder function. At up to 6 months' follow-up, the main outcomes of interest were ICS adherence and days absent from school for any reason.

Children assigned to inhaler reminders had greater ICS adherence: median 84%, compared to 30% in the control group. There was no difference in missed school days, however: 1.9% and 1.7%, respectively. Reminders were associated with a greater reduction in asthma morbidity score: from 9.3 to 7.3 in the intervention group versus 9.2 to 8.0 in the control group. There was a significant difference in parent-reported exacerbations at 2 months, 7% versus 24%; but not at 4 or 6 months.

Audiovisual reminders using the SmartTrack device improve ICS adherence in school-age children with recent ED visits for asthma. The reminders also improve several measures of asthma control, but have no apparent effect on school absences. In patients with poorly controlled asthma, the benefits of improved symptom control will likely offset the initial cost of the electronic monitoring device.

COMMENT: *In a recent editorial (J Allergy Clinical Immunol. 2014;134:1269-1270), Eric Bateman reinforced that improving adherence to controller therapy may be the "last frontier" in asthma treatment of asthma. Thus, this study by Chan and colleagues could not come at a better time. In an attempt to improve adherence among asthmatic children, the authors evaluated the SmartTrack device, which provides an audiovisual reminder of twice-daily ICS dosing, as well as recording adherence. In this large randomized trial, children assigned to the reminder group had significantly greater adherence, improved morbidity score, and reduced rescue medication use. Unfortunately, there was no reduction in further emergency care or in missed school days or caregiver work absences. The authors note that the study was underpowered to detect these differences. They acknowledge that the SmartTrack device is not cheap ($230 in 2013), but hope that future advancements will reduce the cost. The authors further speculate that the cost-effectiveness of using such a device could be increased by making use of it in poorly controlled asthmatics—specifically, those recently requiring ED care.*

J.J.O.

Chan AHY, Stewart AW, Harrison J, et al: The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomized controlled trial.

Lancet Respir Med. 2015;3:210-219. ♦♦

Synergistic Effect of Beta-Blockers and ACE Inhibitors on Anaphylaxis

DRUGS are an important class of "cofactors" that interact with triggering allergens to elicit anaphylaxis. Beta-blockers and angiotensin-converting enzyme (ACE) inhibitors are widely used cardiovascular drugs that might aggravate anaphylactic responses. These two drug classes were evaluated as possible cofactors for anaphylaxis in a mouse model.

An initial database study suggested an increased risk of severe anaphylaxis in people taking either beta-blockers or ACE inhibitors alone, with an even more pronounced effect when the two drugs were used in combination. Mouse models of anaphylaxis were used to assess the in vivo interactions of the beta-blocker metoprolol and the ACE inhibitor ramipril on the severity of anaphylactic responses. Further studies in bone marrow-derived mast cells were performed to identify the mechanism by which these drugs may act as anaphylaxis cofactors.

In the mouse models, ramipril alone had no effect on anaphylactic response, while metoprolol had only a modest aggravating effect. However, in combination the two types of cardiovascular drugs strongly augmented the anaphylactic reactions. The two drugs also enhanced mast cell mediators, including a synergistic increase in FcεRI-mediated mast cell histamine release. This mast cell priming effect was more pronounced when FcεRI aggregation was in the suboptimal range, consistent with clinical observations.

The experimental results support the epidemiologic findings suggesting that the combination of beta-blockers and ACE inhibitors may aggravate anaphylactic responses. The study provides evidence of a synergistic effect involving a decreased threshold of mast cell activation. Given the widespread use of these cardiovascular medications, the findings may have important clinical implications.

COMMENT: *This unique report correlates clinical observations with laboratory findings in a mouse model. Treatment with either beta-blockers or ACE inhibitors resulted in a higher risk for severe anaphylaxis, but when the two drugs were used together, the effect was even more pronounced. Laboratory studies confirmed that the combination of beta-blocker and ACE inhibitor had a synergistic effect of enhancing histamine release from mast cells. We should be extra cautious with our patients who are at increased risk for anaphylaxis when they are receiving both beta-blockers and ACE inhibitors.*

S.M.F.

Nassiri M, Babina M, Dölle S, et al: Ramipril and metoprolol intake aggravate human and murine anaphylaxis: evidence for direct mast cell priming.

J Allergy Clin Immunol. 2015;135:491-499. ♦♦

ICS in COPD: Sometimes More Harm than Good!

STUDIES have reported that anti-inflammatory therapy with inhaled corticosteroids (ICS) can improve symptoms and reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD). Other studies have found an increased incidence of pneumonia among COPD patients using ICS, although without an increased risk of pneumonia-related or overall mortality. The authors review the literature on pneumonia, mortality, and ICS use in patients with COPD.

Most relevant studies, including randomized trials, have reported a substantial risk of pneumonia associated with ICS therapy for COPD. However, the randomized trials have been limited by their reliance on adverse event reporting, without systematic ascertainment of pneumonia. Observational studies have often included radiographic assessment of pneumonia, but have been limited by their retrospective design.

Reports have suggested a dose-effect relationship, with higher unadjusted risks of pneumonia in patients taking more potent ICS formulations, with longer durations of use and higher doses. But despite the strong and consistent association with pneumonia, all studies have found no difference or a reduction in pulmonary or overall morality in ICS users. The patterns are consistent with a "double effect": while ICS may predispose COPD patients to an increased risk of pneumonia, there appears to be some offsetting protective effect against mortality.

This double effect might account for the apparently conflicting findings on ICS in patients with COPD. This issue can only be settled by prospective studies including pneumonia as a prespecified outcome, with systematic assessment and monitoring.

COMMENT: *Although it has become fashionable to aggressively prescribe asthma medications in COPD, a significant body of literature has emerged regarding the lack of efficacy and potential safety signals with ICS in patients with COPD. The best marker for favorable response to ICS is eosinophilic airway inflammation. The allergist is the appropriate specialist to make this determination.*
B.E.C.
Festic E, Scanlon PD: Incident pneumonia and mortality in patients with chronic obstructive pulmonary disease. A double effect of inhaled corticosteroids?
Am J Respir Crit Care Med. 2015;191:141-148. ♦♦

REVIEWS OF NOTE

COMMENT: *This excellent and comprehensive review succinctly captures the up-to-date management of exercise-induced bronchoconstriction and asthma in athletes. With the increased participation of individuals in competitive sports, these specific recommendations for high-level athletes are very handy--although based largely on expert opinion.*
C.D.
Boulet L-P, O'Byrne PM: Asthma and exercise-induced bronchoconstriction in athletes.
N Engl J Med. 2015;372:641-648. ♦♦

COMMENT: *Persistent cough in children can be maddening for the patient and challenging for the provider to address. This case documents the presence of pertussis in a 16-year-old boy with springtime intractable cough, despite complete immunization per current recommendations. This increasingly prevalent occurrence raises the question of whether additional doses of TDaP are needed to maintain immunity, secondary to waning of the protective effect of the acellular pertussis vaccine.*
C.D.
Wessels MR, Brigham KS, DeMaria A Jr: Case 6-2015: a 16-year-old body with coughing spells.
N Engl J Med. 2015;372:765-773. ♦♦

COMMENT: *With an increased number of states legalizing marijuana, allergists are more likely to see patients with sensitization to cannabis. This review describes patients with atopy to cannabis in the forms of allergic rhinitis, asthma, conjunctivitis, and anaphylaxis. The authors remind us that immunocompromised patients may be at risk of invasive disease from cannabis contaminated with fungi. Extracts for testing can be made from the leaves or flowers for skin prick testing. Cases of treatment with immunotherapy have also been described. As cannabis use increases, allergists should consider the possibility of atopy in patients who are symptomatic.*
V.H.T.
Ocampo TL, Rans TS: Cannabis sativa: *the unconventional "weed" allergen.*
Ann Allergy Asthma Immunol. 2015;114:187-192. ♦♦

COMMENT: *This British guideline is a wonderful tool for the practicing allergist. It provides a useful algorithm in the evaluation of penicillin allergy. Its greatest utility may be the section on cephalosporins and cross-reaction between these agents.*
J.J.O.
Mirakian R1, Leech SC, Krishna MT, et al: Management of allergy to penicillins and other beta-lactams.
Clin Exp Allergy. 2015;45:300-327. ♦♦