

FEATURE ARTICLES

Peanut Oral Immunotherapy Combined with Probiotics: Closer to a Cure?

A recent study reported promising results with a combined probiotic and peanut oral immunotherapy (PPOIT) approach in children with peanut allergy. The authors report 4-year clinical and immunologic outcomes in children assigned to PPOIT.

The analysis included data from 48 of 62 children with peanut allergy randomly assigned to 18 months of PPOIT or placebo treatment. Active treatment included the probiotic *Lactobacillus rhamnosus* plus peanut oral immunotherapy; controls received two formulations of maltodextrin. Allergy outcomes, skin prick tests, and specific IgE levels were evaluated a mean of 4.2 years after the end of treatment.

In the original trial, PPOIT led to higher rates of peanut

desensitization and 2-week sustained unresponsiveness. At follow-up, children receiving PPOIT were more likely to have continued peanut consumption: 67% versus 4%, with a number needed to treat (NNT) of 1.6. Allergic reactions to peanut, none anaphylactic, occurred in 4 children in the PPOIT group and 6 in the placebo group. Active treatment was associated with smaller wheal size, mean 8.1 versus 13.3 mm; and a higher sIgG4:sIgE ratio, geometric mean 67.3 versus 5.2. On double-blind, placebo-controlled food challenge, 58% of the POIT group attained 8-week sustained unresponsiveness versus 7% of the placebo group: NNT 1.9.

A regimen of combined peanut oral immunotherapy and probiotic treatment shows lasting clinical improvement and suppression of food-specific immune response in children with peanut allergy. The findings suggest that "tolerance is a realistic target for food allergy treatments." The authors plan further studies, including assessment of PPOIT's effects on the gut microbiome. ● ● ●

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COMMENT: This study by Hsiao and colleagues is very exciting for the allergy community. In the placebo-controlled trial, probiotics administered in tandem with peanut oral immunotherapy resulted in long-lasting peanut tolerance 4 years after discontinuation of treatment. Two-thirds of actively treated patients were able to continue regular ingestion of "moderate-to-large" amounts of peanut on a regular basis, compared to 4% of the placebo group. This would indicate that sustained unresponsiveness can be attained. Although there are several methodologic issues that must be overcome with future studies, these provocative results provide hope that a cost-effective cure for peanut allergy may be on the horizon.

J.J.O.

Hsiao K-CH, Ponsonby A-L, Axelrad C, et al: Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial.

Lancet Child Adolesc Health. 2017; 1:97-105. ●

Keywords: microbiome, oral immunotherapy, peanut allergy, probiotics

Another Look at LEAP

The "Learning Early About Peanut Allergy" (LEAP) study found a lower risk of peanut allergy among high-risk children assigned to early introduction of peanut at 4 to 11 months old. Questions remain about how the response to early introduction is affected by variables such as baseline wheal size and age at introduction. These issues were addressed in a secondary analysis of publicly available LEAP datasets.

The analysis included all 640 LEAP subjects with complete available data including 60-month oral peanut challenge results. Factors affecting achievement of peanut tolerance were assessed, including baseline sensitization to peanut and egg; the presence, severity, and duration of eczema; age at peanut introduction; and gender and race.

In a multiple logistic regression model, children in the early introduction arm were nine times more likely to tolerate peanut at age 60 months: odds ratio (OR) 9.2. Other factors associated with peanut tolerance were white race, OR 2.1; older age at introduction, OR 4.4. Peanut tolerance was less likely for children with larger peanut wheal size, OR 0.58; more severe atopic dermatitis at baseline, OR 0.98; and higher egg-specific IgE, OR 0.99.

Among children with a baseline peanut wheal size of less than 4 mm, peanut tolerance was achieved in 83% of the early introduction group versus 43% of the allergen avoidance group. In several models, peanut tolerance was more likely to be achieved with peanut introduction at 6 to 11 months, compared with 4 to 6 months. Greater eczema severity had little impact on achievement of peanut tolerance after early introduction.

In infants at high risk of peanut allergy, the effect of baseline wheal size on peanut tolerance at 60 months is much stronger in children assigned to allergen avoidance, compared to early introduction. The benefits of early introduction appear greatest when peanut is introduced at 6 to 11 months, rather than before 6 months. The authors discuss the clinical implications for early peanut introduction.

COMMENT: In this secondary analysis of the LEAP dataset, Greenhawt and colleagues found that peanut introduction ● ● ●

between 6 and 11 months of life was associated with a higher probability of successful oral food challenge at 60 months, compared to before 6 months. Overall, these data strongly reinforce the risk-reducing effect of early peanut introduction. They also provide reassurance that, for children in whom there is concern about possible peanut sensitization, there is a larger window of opportunity for effective peanut introduction.

J.J.O.

Greenhawt M, Fleischer DM, Chan ES, et al: LEAPing through the looking glass: secondary analysis of the effect of skin test size and age of introduction on peanut tolerance after early peanut introduction.

Allergy. 2017;72:1254-1260. ●

Keywords: early introduction, peanut allergy, prevention

nitric oxide levels. The latter two outcomes were achieved concurrently with lower rates of clinically significant asthma exacerbations. These changes in biomarker levels suggest that tezepelumab has important effects on Th2 cytokine pathways. Notably, the clinical end points attained were independent of baseline eosinophil count. Since nonallergic factors such as tobacco smoke, diesel particles, and viruses also trigger TSLP release and incite activation of inflammatory responses in asthma, one can hope that this therapy may have a broader impact.

C.D.

Corren J, Parnes JR, Wang L, et al: Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;210:936-946. ●

Keywords: asthma (adult), biologics, uncontrolled asthma

Anti-TSLP Biologic Shows Promise in Uncontrolled Asthma

Some patients have moderate to severe asthma that cannot be controlled by current treatments, especially those with a noneosinophilic pattern of airway inflammation. Initial trials suggested that tezepelumab, an IgG2 monoclonal antibody that binds to thymic stromal lymphoprotein (TSLP), inhibited asthmatic responses and suppressed markers of type 2 inflammation in subjects with mild allergic asthma. This phase 2 trial evaluated tezepelumab in patients with uncontrolled asthma.

The randomized trial included 584 patients with uncontrolled asthma despite long-acting beta-agonists and medium- to high-dose inhaled corticosteroids. Three groups received subcutaneous tezepelumab at a dose of 70 mg every 4 weeks, 210 mg every 4 weeks, or 280 mg every 2 weeks. Controls received placebo. Asthma exacerbation rate and other outcomes were assessed after 52 weeks of treatment.

Annualized asthma exacerbation rates (in events per person-year) were 0.26 with low-dose, 0.19 with medium-dose, and 0.22 with high-dose tezepelumab, compared to 0.67 in the placebo group. The benefits of tezepelumab were unrelated to baseline eosinophil count. Active treatment also led to a higher prebronchodilator FEV₁. The tezepelumab groups had significant reductions in blood eosinophils, exhaled nitric oxide, and total serum IgE. Adverse events were similar across groups; there were 3 serious adverse events attributed to tezepelumab.

Anti-TSLP therapy with tezepelumab is associated with fewer exacerbations in adults with uncontrolled asthma. This benefit is independent of baseline eosinophil count, and is accompanied by reductions in inflammatory biomarkers. The researchers suggest, "[T]argeting an upstream cytokine such as TSLP...may affect disease activity more broadly than inhibition of a single downstream pathway."

COMMENT: In this phase 2 study, tezepelumab reduced total serum IgE levels, blood eosinophil counts, and exhaled

Dust Mite Avoidance Works After All

Many children with asthma are sensitized to house dust mite (HDM). Allergen exposure, in synergy with viral infection, is an important risk factor for exacerbation and hospital admission. This randomized trial evaluated the benefits of mite-impermeable bedcovers for HDM-sensitized children with asthma.

The UK study included 284 mite-sensitized children with asthma exacerbations who were seen in the emergency department (ED). More than two-thirds of the children were boys; mean age was 7.7 years. Patients were randomized to receive a mite-impermeable bedcover or a control/placebo bedcover. At 12 months, the occurrence of severe asthma exacerbations was compared between groups.

Children who received mite-impermeable bedcovers had a lower rate of emergency department visits for asthma exacerbation: 29.3%, compared to 41.5% for those receiving placebo bedcovers. On multivariable analysis, the hazard ratio for hospital visits for exacerbations was 0.55 in the active treatment group. There was also a 27% reduction in ED visits, but the difference was not significant. There was also no difference in exacerbations requiring prednisolone. Levels of Der p 1 in mattress dust were 84% lower for children receiving mite-impermeable bedcovers.

Allergen-impermeable bedcovers can reduce ED visits for exacerbations in asthmatic children with HDM allergy. The bedcovers cost about \$200; the authors estimate that providing 8 children with mite-impermeable bedcovers would prevent one patient from a hospital visit in the subsequent year.

COMMENT: Childhood asthma is associated with a high rate of HDM allergy. When mites are controlled, bronchial hyper-reactivity decreases. In the present study, this strategy resulted in a highly significant decrease in levels of major HDM allergen (Der p 1). There was a 45% decrease in exacerbations requiring acute treatment compared to placebo. However, there was no statistically significant difference regarding the use of prednisolone. This "one-time," ●●●

low-cost intervention does not require prior authorization or co-pays and should be discussed with patients.

B.E.C.

Murray CS, Foden P, Sumner H, et al: Preventing severe asthma exacerbations in children: a randomized trial of mite-impermeable bedcovers.

Am J Respir Crit Care Med. 2017;196:150-158. ●

Keywords: asthma (child), dust mite allergy, exacerbations

ing a corticosteroid "burst," while considering alternative options.

D.M.L.

Waljee AK, Rogers MAM, Lin P, et al: Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ. 2017;357:j1415. ●

Keywords: adverse effects, oral corticosteroids

Steroid Bursts Carry Risks

In contrast to chronic use, little is known about the potential for harmful effects of short-term corticosteroid use. This is especially important in the many common conditions where short courses of corticosteroids are given in the absence of evidence for efficacy. This population-based cohort study assessed adverse events associated with short-term oral corticosteroid use.

The analysis included more than 1.5 million adults, aged 18 to 64, continuously enrolled in a nationwide private insurance database from 2012 to 2014. Of these, 327,452 patients received at least one outpatient prescription for oral corticosteroids lasting less than 30 days: a rate of 21.1%. Median treatment course was 6 days and median prednisone equivalent daily dose 20 mg/d. The most common indications were upper respiratory infections, spinal conditions, allergies, bronchitis, and lower respiratory disorders.

The most frequent adverse events were fractures, 21 events for 1,000 users per year; venous thromboembolism, 5 events per 1,000 users per year; and hospitalization for sepsis, 2 events per 1,000 users per year. In a self-controlled case series, incidence rate ratios within 30 days of drug initiation were 5.30 for sepsis, 3.33 for venous thromboembolism, and 1.87 for fracture. These risks were also significant among patients with prednisone equivalent doses of less than 20 mg/d. Risks decreased from 31 to 90 days after steroid initiation.

In this nationwide insurance database, more than 20% of nonelderly adults received short-term oral corticosteroids over three years. Short-term oral corticosteroids are associated with substantially increased risks of serious adverse events. The researchers conclude, "Greater attention to initiating prescriptions of these drugs and monitoring for adverse events may potentially improve patient safety."

COMMENT: The consequences of long-term corticosteroid use are well documented. This study demonstrates that short-term exposure is not innocuous. The most common exposure observed was a six-day methylprednisolone "dosepak"—accounting for almost half—and the most frequent indication was upper respiratory infection. The study likely underestimates the true impact of short-term corticosteroids, as it examined only a limited number of adverse events. These data should not lead us to stop prescribing corticosteroids. However, they should remind us to carefully assess the potential for benefit versus harm before prescribing

Anti-IgE Therapy for Urticaria: Let's Get Physical

Cold urticaria—accounting for one-third of cases of physical urticaria—is a serious condition with a high risk of systemic reactions. Some patients have persistent signs and symptoms despite high doses of antihistamines. The authors report a randomized trial of anti-IgE therapy with omalizumab for refractory cold urticaria.

The phase 2, multicenter trial included 31 patients with cold urticaria that did not respond to antihistamines. Patients were randomly assigned to omalizumab, 150 or 300 mg, or placebo. Enrollment was halted when interim analysis showed clinically and statistically superior outcomes with omalizumab.

Critical temperature threshold at 10 weeks was -10.6°C with the 150 mg dose of omalizumab and -10.4°C with the 300 mg dose, compared to -0.3°C with placebo. Threshold values improved within 4 weeks after the start of treatment. Complete response rates were 40% with omalizumab 150 mg and 44% with omalizumab 300 mg, compared to zero with placebo. Adverse effects were similar across the three groups.

This small randomized trial shows high response rates to omalizumab in patients with refractory cold urticaria. In contrast to studies of chronic spontaneous urticaria, outcomes are similar with the 150 and 300 mg omalizumab doses. The strong responses observed suggest a pathogenetic role of IgE in cold urticaria.

Symptomatic dermographism (SDerm) is the most common form of physical urticaria, causing lasting impairment in quality of life. This randomized trial evaluated omalizumab anti-IgE therapy for patients with antihistamine-refractory SDerm.

Sixty-one patients with SDerm that did not respond to uposing of antihistamines were randomly assigned to omalizumab 150 or 300 mg or placebo. At baseline, SDerm was having a very large impact on the patients' quality of life.

The primary outcome of critical friction threshold at week 10 decreased by about 2 units (on a 0-to-4 scale) in the omalizumab groups, compared to 0.6 units with placebo. Friction thresholds rose again after omalizumab treatment stopped. Complete response rates were 44% with ●●●

omalizumab 150 mg and 53% with omalizumab 300 mg, compared to 11% with placebo.

Adverse events were similar in the omalizumab and placebo groups. A minimal clinically significant improvement in quality of life was achieved in 72% of patients with omalizumab 150 mg and 58% with omalizumab 300 mg, compared to 32% with placebo.

The results show statistically and clinically significant improvement in disease activity in patients with refractory SDerm treated with omalizumab. As in cold urticaria, further study is needed to clarify the impact of omalizumab dose and the pathogenetic role of IgE.

COMMENT: The randomized controlled trials (RCTs) that led to FDA approval of omalizumab for chronic urticaria excluded subjects with physical urticaria. The evidence supporting a therapeutic role of omalizumab for physical urticaria syndromes has been based on case series and case reports. These two RCTs demonstrate statistically and clinically significant benefit in patients with dermatographia and cold urticaria. They provide high-quality evidence that omalizumab can have a salutary effect in patients whose condition is not controlled by high-dose antihistamines. The lack of difference in response to the 150 and 300 mg doses merits clarification in further studies.

D.M.L.

Metz M, Schütz A, Weller K, et al: Omalizumab is effective in cold urticaria—results of a randomized placebo-controlled trial. *J Allergy Clin Immunol.* 2017;140:864-867.

Maurer M, et al: Omalizumab is effective in symptomatic dermatographism—results of a randomized placebo-controlled trial.

J Allergy Clin Immunol. 2017;140:870-873. ●

Keywords: biologics, chronic urticaria, omalizumab, physical urticaria

both CRSsNP and CRSwNP, compared to a 7.4-fold difference between control and AERD specimens. The AERD specimens also showed a 3.5-fold difference in platelet MPs and a 2.5-fold difference in basophil MPs.

Basophil activation, based on mean fluorescence intensity of CD203c on MPs, was significantly increased in the CRSwNP and AERD groups, but not in the CRSsNP group. Epithelial cell MPs positive for epithelial cell adhesion molecule were similar in the CRSwNP and control groups, but lower than in the CRSsNP and AERD groups.

Analysis of MPs in nasal lavage fluids suggests increased mast cell, platelet, and basophil activation in patients with AERD, compared to those with CRS. The results indicate that CRSwNP is associated with less epithelial injury compared to CRSsNP and AERD. The authors discuss the potential use of MP biomarkers to assess phenotypes of CRS, including the clinically important distinction between AERD and CRSwNP.

COMMENT: Microparticles are extracellular vesicles released from the plasma membrane of cells during activation and have been used as an indicator for apoptosis. These researchers collected nasal lavage fluid to investigate the differences in MPs in patients with CRS and AERD. Mast cell, platelet, and basophil MPs were higher in AERD than in CRS but there were clear differences in the MP findings among phenotypes. The authors suggest that levels of various MPs could serve as biomarkers to distinguish AERD from CRS, particularly with nasal polyps.

S.M.F.

Takahashi T, Kato A, Berdnikov S, et al: Microparticles in nasal lavage fluid in chronic rhinosinusitis: Potential biomarkers for diagnosis of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol.* 2017;140:720-729. ●

Keywords: AERD, biomarkers, chronic rhinosinusitis

FOCUS ON BIOMARKERS

Microparticles: Potential New AERD Biomarker?

Microparticles (MPs) are nanoscale extracellular vesicles released by activated or injured cells. Previous studies have reported the use of MPs as biomarkers of cell injury or activation, including apoptosis. The authors evaluated MPs in nasal lavage fluids as biomarkers of aspirin-exacerbated respiratory disease (AERD), particularly as distinguished from chronic rhinosinusitis with nasal polyps (CRSwNP).

The study included nasal lavage specimens from 33 patients with chronic rhinosinusitis without nasal polyps (CRSsNP), 45 with CRSwNP, 31 with AERD, and 24 controls. Endothelial, epithelial, platelet, eosinophil, mast cell, and basophil MPs were compared by flow cytometry.

Control specimens showed increased activated mast cell MPs—positive for CD137, FcεRI, and c-kit—compared to all three patient groups. Differences were 2.3-fold compared to

Bronchial Microbiome Patterns: New Phenotypic Biomarkers?

Recent reports have suggested that the bronchial microbiome differs between asthma patients and controls, and may affect the asthma phenotype. It is unclear whether these associations are related to asthma itself, to aeroallergen sensitization, or to inhaled corticosteroid therapy. This study compared the bronchial microbiome in adult asthma patients, atopic patients without asthma, and healthy controls.

The researchers obtained bronchial brush specimens from 42 steroid-naïve patients with atopic asthma, 21 patients with atopy but not asthma, and 21 nonatopic controls. Bronchial microbiota profiling was performed using 16S rRNA gene sequencing, and compositional and functional differences related to asthma were assessed. Associations with important differences in asthma phenotype were evaluated, including markers of type 2-related inflammation and changes in airway hyperresponsiveness after 6 weeks on inhaled fluticasone. ● ● ●

Despite some overlap with the atopic, nonasthmatic group, the microbiome in asthma patients was associated with enrichment of the genera *Haemophilus*, *Neisseria*, *Fusobacterium*, and *Porphyromonas* and the family Sphingomonadaceae; as well as depletion of the family Mogibacteriaceae family and the order Lactobacillales. These differences were predicted to affect functions involving amino acid and short-chain fatty acid metabolism pathways.

Within the asthmatic group, the airway bacterial burden was lower among patients meeting criteria for "T2-high"-type asthma. Responsiveness to inhaled fluticasone was associated with distinct microbiome changes, including increases in Microbacteriaceae and in *Neisseria* and *Moraxella* species and depletion of a specific *Fusobacterium* species.

The study shows distinct changes in the airway microbiome associated with asthma, and with important immunologic and clinical asthma characteristics. The authors conclude, "The specific differences identified suggest possible microbiome targets for future approaches to asthma treatment or prevention." They call for further studies to clarify the microbial factors associated with asthma and atopy.

COMMENT: Recent reports suggest that patients with severe asthma have an inverse relationship between their bronchial bacterial burden and bronchial eosinophils. This well-designed study from the NHLBI AsthmaNet found significant compositional and functional differences in the bronchial bacterial microbiomes in Th2 asthmatics and allergic nonasthmatics compared to controls. Interestingly, the Th2 patients had a reduced bronchial bacterial burden, compared to those considered "type 2 low." There were also variations in the bronchial microbiota between steroid-responsive and steroid-nonresponsive patients. The authors suggest that microbiome targets might be useful for either asthma therapy or prevention.

S.M.F.

Durack J, Lynch SV, Nariya S, et al: Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. *J Allergy Clin Immunol*. 2017;140:63-675. ●

Keywords: asthma (adult), biomarkers, corticosteroid response, microbiome

A Urine Dipstick Test for Aspirin-Intolerant Asthma?

Previous studies have reported that urinary leukotriene E4 (LTE4) is increased during asthma exacerbations, as well as in response to challenge with allergens and with nonsteroidal anti-inflammatory drugs. The authors performed a meta-analysis of the evidence for ULTE4 as a potential biomarker for aspirin-intolerant asthma.

A systematic review of the literature identified 10 clinical studies evaluating ULTE4 as a test for identifying patients with the aspirin-intolerant asthma phenotype. The criteria for identifying patients with aspirin-intolerant asthma were a convincing history of aspirin intolerance and/or positive aspirin challenge.

In general, ULTE4 was higher for asthma patients versus controls, and higher for patients with aspirin-intolerant versus aspirin-tolerant asthma. Studies using the mass spectrometry (MS) and radioimmunoassay (RIA) showed higher ULTE4 in patients with aspirin-intolerant versus aspirin-tolerant asthma.

Diagnostic performance varied between the different assays used. Sensitivity, specificity, and positive and negative predictive values were 0.55, 0.82, 0.75, and 0.66 for the Amersham-enzyme immunoassay; 0.76, 0.77, 0.70, and 0.78 for the Cayman-enzyme immunoassay; 0.70, 0.81, 0.86, and 0.79 for MS; and 0.81, 0.79, 0.65, and 0.88 for RIA. These values reflected optimal thresholds of 192, 510, 167 to 173, and 66 to 69 pg/mg Cr, respectively. Diagnostic odds ratios for detecting aspirin intolerance in asthma patients were 6.0, 11.9, 10.5, and 19.1.

Assembled evidence suggests that ULTE4 could be a useful biomarker to identify patients with aspirin-sensitive asthma. The authors emphasize the need for efforts to develop age- and sex-based norms for ULTE4, and for prospective studies to define its clinical value for specific asthma phenotypes.

COMMENT: This is the first systematic review focusing on the diagnostic accuracy of ULTE4 for ASA-intolerant asthma. The authors found optimal threshold values for the various methods/immunoassays used to detect LTE4. They conclude that ULTE4 could potentially be used as a clinical test to detect patients with potential ASA-intolerant asthma. The authors recommend continued research to further refine age- and sex-based normative values.

J.J.O

Hagan JB, Laidlaw TM, Divekar R, et al: Urinary leukotriene E4 to determine aspirin intolerance in asthma: a systematic review and meta-analysis.

J Allergy Clin Immunol Pract. 2017;5:990-997. ●

Keywords: AERD, aspirin-intolerant asthma, biomarkers, phenotypes

Mucin as Biomarker for Chronic Bronchitis

Mucin concentration on airway surfaces might play a role in the development of mucus transport problems in muco-obstructive lung diseases. This study evaluated the contribution of high mucin concentration to sputum production/characteristics and disease progression in chronic bronchitis.

The study included 917 patients from the "Subpopulations and Intermediate Outcome Measures in COPD Study" (SPIROMICS). Evaluations included questionnaires, chest imaging, lung function studies, and induced sputum examination. In sputum samples, total mucin concentration was measured using size-exclusion chromatography and refractometry.

A subgroup of 148 subjects underwent measurement of the respiratory-secreted mucins MUC5AC and ●●●

MUC5B via mass spectrometry. An independent cohort of 94 subjects with or without chronic bronchitis also underwent measurement of total mucin in sputum.

Mean total mucin concentration was 3,166 $\mu\text{g}/\text{mL}$ in current or former smokers with severe COPD, compared to 1,515 $\mu\text{g}/\text{mL}$ in controls who had never smoked. Total mucin was also elevated in subjects with at least two exacerbations in the previous year, compared to those with no exacerbations: 4,194 versus 2,458 $\mu\text{g}/\text{mL}$. In the subgroup analysis, MUC5B was 3 times higher and MUC5AC was 10 times higher in subjects with severe COPD, compared to never-smoking controls. Area under the receiver operating characteristic curve for total mucin versus diagnosis of chronic bronchitis was 0.72 in the SPIROMICS cohort and 0.92 in the independent cohort.

Airway mucin may be a central contributor to sputum development and disease severity in chronic bronchitis. With confirmatory studies, airway mucin could be a useful biomarker for diagnosis of chronic bronchitis, and possibly a new therapeutic target.

COMMENT: Chronic bronchitis is an important risk factor for the development and progression of COPD. Kesimer et al demonstrate that airway mucins are related to smoking, respiratory symptoms, and disease severity and exacerbations in COPD. Asthma is also associated with increased mucus hypersecretion: approximately 15% of current or former smokers in the SPIROMICS cohort reported current asthma and had higher airway mucin levels than controls. A diagnosis of childhood asthma is also associated with higher mucin levels, despite the lack of a demonstrable relationship between airway mucin levels and asthma biomarkers. These results open the door for further studies targeting mucins.

C.D.

Kesimer M, Ford AA, Ceppe A, et al: Airway mucin concentration as a marker of chronic bronchitis. *N Engl J Med.* 2017;377:911-922. ●

Keywords: biomarkers, bronchitis, COPD, mucin

Probiotics in Your Mattress Cover...Really?

Allergen avoidance is commonly recommended for patients with allergic rhinitis (AR) and house dust mite allergy. Previous trials of impermeable bedding covers, alone or with other avoidance measures, have shown little benefit in reducing AR symptoms. This pilot study evaluates a new type of bedding cover impregnated with probiotics.

The trial included 20 adults with AR, with confirmed house dust mite allergy and presence of Der p 1 in bedding dust samples. In crossover fashion, patients used probiotic-impregnated Purotex bedding covers and untreated placebo bedding covers for 8 weeks.

The two bedding covers led to similar reductions in Der p 1 in mattress and pillow dust samples, the primary study outcome. The probiotic-impregnated bedding covers also led to improvement in some AR symptom and quality of life (QOL)

scores compared to baseline, which were not observed with the untreated covers. However, the differences in these outcomes were not significantly different between the intervention and control periods.

The results show significant improvement in some AR symptoms and QOL scores with probiotic-impregnated bedding covers for patients with house dust mite allergy. This is despite the lack of difference in Der p 1 levels. A larger trial might show a significant difference in clinical outcomes.

COMMENT: Studies of bedding covers have been somewhat disappointing in reducing AR symptoms. In laboratory studies, probiotics have reduced Der p 1 levels in fabrics. This small study evaluated clinical effects of probiotic-impregnated bedding covers. Mite allergen levels were reduced in both encasement groups. Although symptoms and QOL were better with probiotics compared to baseline, there was no difference between probiotic and standard encasements. While the study is small, the results are not very impressive and suggest that enhancing encasements with probiotics is of little benefit.

D.A.K.

Berings M, Jult A, Vermeulen H, et al: Probiotics-impregnated bedding covers for house dust mite allergic rhinitis: a pilot randomized clinical trial.

Clin Exp Allergy. 2017;47:1092-1096. ●

Keywords: allergen avoidance, allergic rhinitis, house dust mite, mattress covers

Maternal Stress Affects Long-Term Lung Function In Offspring

Psychologic stress during critical periods could affect lung development, with consequences for lifelong respiratory health. Previous studies of the impact of stress on childhood lung function have yielded mixed results. This issue was addressed using follow-up data on offspring from a pregnancy cohort study.

The study included 106 boys and 93 girls born to women receiving care at a Boston medical center at a mean of 28 weeks' gestation. The women were mainly Hispanic or African American with less than a high school education; 22% were prenatal smokers. An 8-point negative life events (NLEs) score was used to assess maternal stress during pregnancy and at 1 to 2 years postpartum. Maternal stress scores were evaluated for association with the children's spirometry findings at a mean of 7 years old.

Children of mothers with the highest prenatal stress levels—5 or more NLEs—had reduction in several pulmonary function measures. On covariate adjustment, associated z scores were -0.53 for FEV_1 , -0.49 for FVC, and -0.68 for $\text{FEF}_{25\%-75\%}$. The effects were similar for postnatal stress. There was evidence of a larger effect in boys than girls, with z scores of -0.76 for FEV_1 , -0.77 for FVC, and -0.77 for $\text{FEF}_{25\%-75\%}$.

This prospective study suggests that prenatal and postpartum maternal stress has lasting effects on child- ● ● ●

hood lung function. The findings are consistent with impairment of pulmonary growth, greater in boys than girls. Providing resources and support to reduce stress during pregnancy and early childhood might reduce the impact on respiratory health.

COMMENT: We know that stress has adverse effects on health. This study supports prior reports linking maternal stress with persistent wheeze and asthma, and specifically reports an association between maternal stress in the perinatal period and decreased lung function at age 7. Boys appear more susceptible to the stress. Based on these findings, clinicians caring for pregnant women may consider screening for and addressing maternal stress throughout pregnancy and the postpartum period. This further supports the need to address psychological well-being to ensure physical health.

V.H.T.

Lee AG, Chiu Y-HM, Rosa MJ, et al: Association of prenatal and early childhood stress with reduced lung function in 7-year-olds.

Ann Allergy Asthma Immunol. 2017;119:153-159. ●

Keywords: asthma (child), psychologic factors, stress

mental allergens in EoE, including the effectiveness of allergen-specific immunotherapy.

COMMENT: Treatment for EoE can be challenging. Ideally, it would be helpful to predict which patients would respond to therapy. This prospective cohort study found that sensitization to perennial allergens was a marker for lack of response to PPIs. In addition, sensitization to molds and cockroach was associated with poor response to swallowed steroids. As the authors comment, this phenotype may benefit from different treatment, including allergen avoidance. We hope that future studies will clarify the benefits of immunotherapy for patients with EoE.

V.H.-T.

Pesek RD, Rettiganti M, O'Brien E, et al: Effects of allergen sensitization on response to therapy in children with eosinophilic esophagitis.

Ann Allergy Asthma Immunol. 2017;119:177-183. ●

Keywords: aeroallergen sensitization, food allergy, EoE, phenotypes

Can We Predict Treatment Response in Children with EoE?

In addition to foods, aeroallergens might contribute to the development of eosinophilic esophagitis (EoE) in children. Most previous EoE studies have been performed in urban settings. This study assessed the effects of aeroallergen sensitization on response to treatment in nonurban children with EoE.

The researchers analyzed 223 children and adolescents with EoE treated at Arkansas Children's Hospital from 2012 to 2016. Of these, 182 patients underwent assessment of environmental allergen sensitization plus at least one endoscopic examination while on proton pump inhibitor (PPI) therapy. Associations between allergen sensitization and response to EoE therapies were evaluated. Complete response was defined as a peak esophageal eosinophil count of less than 15 per HPF.

The analysis included 129 children, mean age 7.6 years, with EoE that did not respond to PPIs. Of these, 58.5% were complete responders and 26.8% were nonresponders. Perennial allergen sensitization was found in 45.8% of responders compared to 72.7% of nonresponders, but seasonal allergen sensitization was not significantly different between groups. Children sensitized to mold or cockroach were less likely to respond to the combination of dietary elimination and swallowed corticosteroid therapy.

In this nonurban population of children with EoE, sensitization to perennial and mold allergens may affect treatment responses. Environmental allergen sensitization might represent an EoE phenotype that responds to treatment differently. Further studies are needed to clarify the role of environ-

Food Allergy Management: A Must-Read Clinical Vignette

Peanut allergy, affecting about 1% of Americans, is the leading cause of fatal and near-fatal anaphylaxis. The clinical problem and management strategies of peanut allergy are presented in a discussion of a case example.

The patient was a young athlete with peanut allergy and moderate persistent asthma. After a basketball game, he developed cough, shortness of breath, and sneezing in reaction to eating a homemade cookie. Despite a dose of diphenhydramine, his symptoms worsened, including throat tightness and vomiting. He self-treated with epinephrine and four actuations of inhaled albuterol, which relieved symptoms.

The authors review key clinical points of food and peanut allergy, including the criteria for anaphylactic reactions to food allergens. Cutaneous manifestations are most common, but may be absent in 20% of patients with anaphylaxis. Evaluation of food allergy includes a medical history; the authors discuss the role of allergy skin tests, specific IgE measurement, and oral food challenges. They also discuss new guidelines recommending early dietary introduction of peanut to reduce the risk of childhood peanut allergy.

Management options are reviewed, including dietary avoidance, education, and regular follow-up. Epinephrine is the most important medical intervention for food-induced anaphylaxis, but remains "vastly underprescribed and underutilized."

While there is currently no specific treatment, the authors note recent progress toward the development of allergen-specific immunotherapy for food allergy. So far, oral immunotherapy offers the highest rate of clinical desensitization, but also the greatest risk of adverse events. Areas for further research include the reasons for the apparent increase in food allergy prevalence and the optimal short- and ● ● ●

long-term management, including immunotherapy.

COMMENT: This clinical practice vignette describes an 18-year-old basketball player with known peanut allergy and asthma who had an anaphylactic reaction to inadvertent peanut ingestion immediately after playing in a collegiate game. In their inimitable elegant style, Jones and Burks discuss management strategies and weigh the pros and cons of current and future options.

C.D.

Jones SM, Burks AW: Food allergy. *N Engl J Med.* 2017;377:1168-1175. ●

Keywords: food allergy, peanut allergy

FOCUS ON PENICILLIN ALLERGY

Inpatient Penicillin Allergy Testing—Safety and Efficacy Data

True penicillin allergy in hospitalized patients carries risks including longer hospital stay and a higher risk of resistant infections. Inpatient allergy testing can identify patients incorrectly labeled as allergic to penicillin. This meta-analysis evaluated the effects of inpatient allergy testing on clinical outcomes.

A systemic review identified 24 studies of inpatient interventions to assess penicillin allergy during an index admission in which a penicillin antibiotic would be required. Sample size ranged from 24 to 252 patients; the main type of intervention was penicillin skin testing (PST), alone or with oral amoxicillin challenge. Change in antimicrobial therapy was the most commonly reported clinical outcome.

The proportion of patients with negative PSTs ranged from 79% to 100%, with a population-weighted mean of 95.1%. The interventions consistently led to prescribing changes, including increased prescription of penicillin and cephalosporins and decreased use of vancomycin and fluoroquinolones. The changes in antibiotic prescribing were greater in ICU settings: 77.97%, compared to 54.73% in other inpatient settings. Some studies reported cost reductions; rates of adverse effects were very low.

Available data suggest that inpatient penicillin allergy testing leads to favorable changes in antibiotic prescribing and other clinical outcomes. Rates of negative penicillin tests are similar to those reported in outpatient and perioperative studies; the benefits of inpatient testing appear largest in ICU settings. The authors conclude, "Healthcare providers should be empowered to safely perform PST."

COMMENT: This meta-analysis provides additional evidence supporting the utility of immediate hypersensitivity skin testing as an important aspect of the management of hospitalized patients with a history of penicillin allergy. A substantial rise in prescribing of penicillin and cephalosporin antibiotics was observed following PST in this study, more pronounced

in intensive care settings. Penicillin skin testing should be included as a component of a successful antibiotic surveillance program.

D.M.L.

Sacco KA, Bates A, Brigham TJ, et al: Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis.

Allergy. 2017;118:729-731. ●

Keywords: drug allergies, inpatient allergy, penicillin allergy

Further Busting the Penicillin Allergy Mislabeleds

Many children seen in the emergency department (ED) are incorrectly reported as having penicillin allergy. Some reported adverse drug reactions are not consistent with true allergic reactions. This study assessed the presence of high-risk and low-risk symptoms among pediatric ED patients labeled with penicillin allergy.

The study included 500 children seen in a pediatric ED with parent-reported penicillin allergy. A parental questionnaire sought information on age at allergy diagnosis, allergy symptoms, and time from first dose to symptoms. Allergy symptoms were classified as high- or low-risk in consultation with a pediatric allergist, based on organ system involved and the potential for IgE-mediated or T-cell-driven reaction.

Median age at allergy diagnosis was 1 year, and before 3 years in three-fourths of children. Seventy-six percent of children had exclusively low-risk symptoms: most commonly rash (92.8%) and itching (40.6%). The remaining 120 patients had at least one high-risk symptom: most commonly facial swelling (10.0%) and difficulty breathing (7.4%). Symptoms occurred after first exposure to penicillin in 71% of children; ear infection was by far the most common indication. In 54.8% of cases, symptoms began within 24 hours of drug administration.

Most pediatric ED patients with parent-reported penicillin allergy have only low-risk symptoms unlikely to reflect true penicillin allergy. In a subsequent study, the authors report the results of allergy testing in children with low-risk symptoms.

Three-fourths of pediatric ED patients labeled with penicillin allergy have only "low-risk" symptoms for true allergic reactions. The authors report the results of penicillin allergy testing in children with such low-risk symptoms.

The study included 100 children, aged 4 to 18 years, seen at a pediatric ED with parent-reported penicillin allergy. All had only low-risk symptoms for true penicillin allergy—mainly rash and itching—on a parental questionnaire. Penicillin allergy was assessed following a standard three-tier testing process (percutaneous testing, intracutaneous test- ● ● ●

ing, and oral challenge).

Median age was 1 year at allergy diagnosis and 9 years at allergy testing. As hypothesized, all children had negative results on penicillin allergy testing. This included 3 patients with positive results on percutaneous testing. In all 100 patients, the penicillin allergy label was removed from the medical record.

Many pediatric ED patients are incorrectly reported and mislabeled as having penicillin allergy. Using a questionnaire to identify children with "low-risk" symptoms could promote increased use of first-line penicillin antibiotics.

COMMENT: Wow, finally there are data that validate what allergists have known all along: the majority of children who present to the ED with concerns of penicillin allergy have a low risk for true reaction! Also welcome is the creation of a risk stratification questionnaire for penicillin allergy that helps stratify patients as low risk and high risk. This excellent three-tier study conducted at the Children's Hospital of Wisconsin convincingly demonstrates that low-risk allergy symptoms—most commonly rash and itching—likely do not represent true allergy in the pediatric ED. What a gigantic healthcare benefit to all stakeholders to have the penicillin allergy label removed from the medical records!

C.D.

Vyles D, Chiu A, Simpson P, et al: Parent-reported penicillin allergy symptoms in the pediatric emergency department. *Acad Pediatr*. 2017;17:251-255.

Vyles D, Adams J, Chiu A, et al: Allergy testing in children with low-risk penicillin allergy symptoms. *Pediatrics*. 2017;140:e20170471. ●

Keywords: allergy testing, drug allergy, penicillin allergy

Can We Close the Book on the Need for Spacers with pMDIs?

For asthma patients using pressurized metered-dose inhalers (pMDIs), spacers have been recommended to help in coordinating device activation with inhalation. However, there are few data demonstrating the true benefits of spacer use. This study used real-world clinical data to compare outcomes for asthma patients using pMDIs with or without spacers.

Two UK databases were used to identify patients with asthma, age 12 or older, prescribed pMDIs for administration of standard- or extrafine-particle inhaled corticosteroids (ICS). The analysis included matched groups of patients using extrafine-particle ICS (beclomethasone dipropionate, 1,840 in each group) or using fine-particle ICS (fluticasone propionate, 412 in each group), with or without a spacer. A wide range of asthma outcomes were compared.

There was no significant difference in number of severe exacerbations over 1 year for patients with or without a spacer, with both types of ICS. Secondary outcomes were similar as well, including acute respiratory events, risk-domain asthma control, asthma-related hospitalizations or emergency department visits, treatment stability, or incidence of thrush.

Overall asthma control was lower in both spacer groups, possibly driven by a higher rate of short-acting beta-agonist prescribing.

These real-world data show no improvement in clinical outcomes in adolescent and adult asthma patients using pMDIs with a spacer. The findings are similar for patients using standard- or extrafine-particle ICS. The researchers emphasize the need for careful patient education in inhaler technique, with or without a spacer.

COMMENT: Although spacers have been recommended with use of pMDIs for the last 30 years, their utility in the real-world setting has been limited. Thus, this study by Guilbert and colleagues is of great importance. They demonstrated no significant difference in severe exacerbations, respiratory events, or risk-domain asthma control when comparing extrafine-particle or fine-particle ICS with or without a spacer in patients older than 12 years. The findings challenge the belief that spacers increase drug delivery to the lung.

J.J.O.

Guilbert TW, Colice G, Grigg J, et al: Real-life outcomes for patients with asthma prescribed spacers for use with either extrafine- or fine-particle inhaled corticosteroids. *J Allergy Clin Immunol Pract*. 2017;5:1040-1049. ●

Keywords: asthma (adult), exacerbations, inhalers, patient education

The EHR May Actually Be Useful!

Some validated tool is needed to help in assessing the risk of recurrent asthma attacks, ie, severe exacerbations. The authors report the development and performance of a multi-variable prediction model for future asthma attacks, based on an electronic health record (EHR).

The analysis included anonymized EHR data on 118,981 patients, aged 12 to 80 years, receiving active asthma treatment at 400 UK general practices. All patients had at least 3 years of continuous data. Potential risk factors during the first year were evaluated for association with the risk of two or more and four or more asthma attacks—asthma-related emergency department visits, hospitalizations, or oral corticosteroid (OCS) courses—over the following 2 years.

On multiple logistic regression analysis, the strongest predictor of future asthma attacks was the number of OCS courses. Other independent predictors included emergency visits, reliever medication use, health care utilization, lung function, current smoking, blood eosinophilia, rhinitis, nasal polyps, eczema, gastroesophageal reflux disease, obesity, older age, and female sex. The final models comprised 19 risk factors for two or more attacks and 16 risk factors for four or more attacks. Areas under the curve were 0.785 and 0.867, respectively.

Models created using EHR data perform well in identifying patients at high risk of recurrent asthma attacks. With further validation, these models could be useful in identification and guideline-based management of modifiable risk factors for asthma exacerbations.

COMMENT: Analysis of a large dataset revealed inde- ● ● ●

pendent predictors of future asthma attacks. The number of OCS courses had the strongest association; other predictors included frequent use of rescue therapy, healthcare utilization, reduced lung function, current smoking, blood eosinophilia, rhinitis, polyposis, eczema, GERD, obesity, older age, and female sex. What makes this study even more interesting is that it was based on EHR data, demonstrating that an informatics-based approach may aid in risk stratification. Some might argue that this is the only proven use for the EHR.

J.J.O.

Blakey JD, Price DB, Pizzichini E, et al: Identifying risk of future asthma attacks using UK medical record data: A Respiratory Effectiveness Group initiative.

J Allergy Clin Immunol Pract. 2017;5:1015-1024. ●

Keywords: asthma (adult), exacerbations, risk factors

Farm Exposure Linked to Lower Adult Atopy Risk

Previous studies have linked growing up on a farm to a reduced risk of childhood allergy and asthma. Most of these studies have been performed in Europe, while few have examined the allergic disease outcomes in adults. The effects of early-life farm exposure on adult asthma and atopy were assessed in US cohort study.

The Agricultural Lung Health Study included 1,746 farmers and 1,555 spouses, mean age 63 years, from a larger US agricultural cohort. Participants provided information on early-life farming exposure and current asthma in questionnaires; atopy was assessed by measurement of specific IgE levels. Associations between early-life farm exposure and asthma (1,198 cases versus 2,031 controls) and atopy (578 cases and 2,526 controls) were examined by logistic regression, adjusted for age, sex, race, state, and smoking.

Farm exposure in utero and during early childhood was unrelated to asthma in adulthood. However, there were significant protective effects against atopy. The strongest association, odds ratio 0.60, was noted for participants whose mothers performed farm tasks during pregnancy. Reductions in adult atopy with early-life farm exposure remained significant after considering contact with farm animals, raw milk consumption, and other early exposures.

This US study finds a lower risk of atopy among older adults exposed to a farm environment during early-life. The findings support the role of in utero and early childhood exposures in the development of allergic disease. Early-life farm exposure appears to have a lifelong protective effect against atopy, but not asthma.

COMMENT: Previous studies of early-life farm exposures have generally shown a protective effect against allergies and asthma in children. This is the first report to study atopy and asthma in adults in relation to early-life farming exposures. Although farm exposure had little impact on adult asthma, there was some protective effect against adult atopy. Interestingly, having a mother performing farm activities

while pregnant reduced the odds of adult atopy. It seems the protective effect of early-life farming exposures may begin in utero and endure into adulthood.

S.M.F.

House JS, Wyss AB, Hoppin JA, et al: Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study.

J Allergy Clin Immunol. 2017;140:249-256. ●

Keywords: asthma (adult), atopy, farm exposure, hygiene hypothesis

Yet Another Asthma Risk Factor: Being LGA

Infants born large for gestational age (LGA) are at risk of being overweight in childhood, which may place them at increased risk of asthma. Little is known about the association between LGA and childhood asthma. This issue was addressed using data from a birth cohort study, including the effects of atopy.

The study included 1,608 children from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, all with available data on anthropometric measurements and atopic sensitization at age 8. Of these, 12.1% of children were LGA at birth. At 8 years old, 13.3% of children were overweight, 40.6% had atopy, and 8.3% had asthma (including 15.2% of children with atopy and 3.6% of those without atopy).

The association between LGA and asthma was estimated by logistic regression analysis, with adjustment for potential confounders. Being born LGA was not independently associated with childhood asthma. However, children who were born LGA and were overweight at age 8 were at significantly increased risk of asthma: odds ratio (OR) 2.7. The association was even stronger among children without atopy: OR 7.0. On stratification by sex, the association of LGA and overweight with asthma was significant in girls but not boys.

Children who are born LGA and are overweight at age 8 are at increased risk of asthma. The association appears stronger in nonatopic children. The results suggest that children born LGA could be targeted for interventions to prevent childhood overweight, as a means of reducing asthma risk.

COMMENT: Many theories have been raised regarding birth characteristics as risk factors for asthma. Pinto and colleagues note an association between being born LGA, in tandem with being overweight at age 8, and increased odds of having asthma. Although the study population was large (over 1,600), only 214 patients were overweight. The authors reinforce that their findings are preliminary and require validation with larger numbers. Children born LGA may be identified as a high-risk group early in life and may benefit from interventions to prevent being overweight at school age.

J.J.O.

Pinto LA, Guerra S, Anto JM, et al: Increased risk of asthma in overweight children born large for gestational age. Clin Exp Allergy. 2017;47:1050-1056. ●

Keywords: asthma (child), overweight, prevention, risk factors

How Helpful Is Whooping in Diagnosing Pertussis?

The classical symptom triad of whooping cough consists of paroxysmal cough, whooping, and posttussive vomiting. Yet symptom severity may vary widely, leading to challenges in diagnosis. This meta-analysis evaluated the accuracy of clinical symptoms for diagnosis of pertussis in adults and children.

A systematic review of the literature identified 53 papers comparing the clinical characteristics of patients who tested positive versus negative for infection with *Bordetella pertussis*. Of 23,796 patients, 17.3% had a laboratory diagnosis of pertussis. The meta-analysis examined 41 index tests, including nine cough characteristics, for accuracy in pertussis diagnosis in children and adults.

Four factors were important in making or excluding the diagnosis of pertussis in adults. Paroxysmal cough and absence of fever had high sensitivity and low specificity—and thus were useful in "ruling out" pertussis. In contrast, posttussive vomiting and whooping had low sensitivity and high specificity for pertussis in adults—and thus were useful tests for "ruling in" pertussis. Posttussive vomiting was much less helpful; for other tests, estimates of sensitivity and specificity could not be calculated.

The classical symptom triad remains useful for diagnosis of pertussis in adults, but not necessarily in children. The authors note the "substantial statistical heterogeneity" among the studies in their meta-analysis.

COMMENT: Diagnosing pertussis can be a challenge, particularly in adults. This meta-analysis analyzed 53 studies of children and adults to determine symptoms that can help to rule in or rule out a diagnosis of pertussis. In adults, posttussive vomiting or whooping had higher specificity (66% to 78%) for ruling in the diagnosis of pertussis, whereas the presence of fever or paroxysmal cough made the diagnosis of pertussis unlikely. The study was unable to identify reliable clinical markers for diagnosing pertussis in children.

D.A.K.

Moore A, Ashdown HF, Shinkins B, et al: Clinical characteristics of pertussis-associated cough in adults and children: a diagnostic systematic review and meta-analysis. *Chest*. 2017;152:353-367. ●

Keywords: cough, diagnosis, pertussis

Can Rapid Vitamin D Dosing Prevent Asthma Exacerbations in Children?

It has been suggested that vitamin D might reduce the risk of severe exacerbations of childhood asthma. This trial compared rapid versus maintenance vitamin D supplementation strategies for children with asthma exacerbations and low vitamin D levels.

The randomized trial included 231 children, mean 6 years old, seen in the emergency department (ED) with moderate to severe asthma exacerbations and vitamin D levels of 25 ng/mL or less. The rapid supplementation group received an IM injection of vitamin D, followed by daily oral supplementation. The maintenance group received oral vitamin D only. Mean baseline vitamin D levels were 15.1 and 15.8 ng/mL, respectively.

Over 12 months, there was no difference in the primary outcome of unplanned visits for asthma exacerbations. Rapid supplementation did reduce exacerbations during the first 3 months for children with baseline vitamin D levels of 3 to 11 ng/mL: relative rate (RR) 0.48. On analysis of exacerbation frequency per child, the RR was 0.36.

The rapid vitamin D strategy evaluated in this trial may provide short-term reduction in asthma exacerbations for children with the lowest levels of baseline vitamin D. In the longer-term, exacerbation rates are similar with the rapid and maintenance strategies tested. The authors discuss the implications for vitamin D requirements in asthmatic children.

COMMENT: Many studies have looked at vitamin D supplementation in asthma. Overall, the results have been disappointing. This study enrolled children admitted to an ED with asthma exacerbations, checked their vitamin D levels, then randomized them to either a high IM dose plus oral vitamin D or just oral vitamin D. There was only a transient reduction in unplanned asthma visits for the first 3 months of the 12-month study, and only for children with vitamin D levels less than 12 ng/mL. This may have reflected the small sample size in very-low vitamin D group. Since the study was powered to look at the entire time period—with similar results for both groups—the findings are of questionable clinical relevance.

D.A.K.

Alansari K, Davidson BL, Yousef KI: Rapid vs maintenance vitamin D supplementation in deficient children with asthma to prevent exacerbations. *Chest*. 2017;152:527-536. ●

Keywords: asthma (child), exacerbations, vitamin D

REVIEWS OF NOTE

COMMENT: This is a concise clinical review of dual long-acting bronchodilators to relieve exacerbations of chronic obstructive pulmonary disease.

B.E.C.

Beeh KM, Burgel P-R, Franssen FME, et al: How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary disease? *Am J Respir Crit Care Med*. 2017;196:139-149.

COMMENT: This report highlights the importance of considering an "asthma-plus" syndrome in treatment-refractory patients, particularly those with eosinophilia.

C.D.

Divakaran S, Dellaripa P, Kobzik L, et al: All that wheezes . . . *N Engl J Med*. 2017;377:477-484.