NOT FOR CREDIT

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

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FEATURE ARTICLES

SPECIAL COMMENT: We open this issue of *AllergyWatch* with three papers on responding to loss of asthma control. The trial by Jackson et al. had fewer than expected exacerbations, with lack of efficacy after escalation of ICS dose. In contrast, in the pragmatic study by McKeever et al, about half of patients had an exacerbation and ICS dose escalation was efficacious. Why the difference? Possibly with better adherence, there is an overall reduction in exacerbation rate (poor adherence was an exclusion criterion in the Jackson study). Due to the flat dose-response with ICS, even a quadruple dose is not the answer. Unfortunately, in the real world, few of our patients are adherent; when facing loss of asthma control, many patients begin to comply with their controller therapy. Efficacy might improve with increased dosing frequency—for example, twice-daily dosing is more effective than the same dose of ICS given once daily. Therefore the correct answer may be the SMART approach, where more frequent dosing of ICS (tethered to the reliever beta-agonist) might prove most effective. We certainly need to find an answer, as our patients will demand direction when faced with loss of asthma control.

J.J.O.

High-Dose ICS for Exacerbations: No Benefit in Childhood Asthma

Even with conventional inhaled corticosteroids (ICS), children with asthma remain at risk of exacerbations. This randomized trial evaluated a fivefold increase in ICS dose to prevent pediatric asthma exacerbations.

The "Step Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations" (STICS) trial included 254 children, aged 5 to 11, receiving step 2 therapy for mild-to-moderate persistent asthma. Over 52 weeks, all received open- • • •

FEATURE ARTICLES

SANOFI GENZYME REGENERON

This activity is supported by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

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 Asthma
- 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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label low-dose maintenance ("green zone") therapy with fluticasone: 44 μg 2 puffs bid. When signs of loss of asthma control appeared ("yellow zone"), the children either continued low-dose ICS or received high-dose therapy with fluticasone 220 μg 2 puffs bid versus fluticasone for 7 days. Rates of severe exacerbations requiring systemic glucocorticoids were compared during blinded treatment with low-dose versus high-dose ICS.

One or more severe exacerbations occurred in 38 children in the high-dose group and 30 in the low-dose group; the difference was not significant. The two groups were also similar in time to first severe exacerbation, emergency or urgent care visits for asthma, and symptom burden during yellow-zone episodes. During the study year, growth rate was 0.23 cm less in the high-dose ICS group.

For school-age children with persistent asthma, quintupling the dose of ICS during yellow-zone periods does not reduce severe exacerbations or improve other clinical outcomes. The authors note that the rates of yellow-zone episodes and severe exacerbations requiring systemic glucocorticoids were lower than expected.

COMMENT: The management of acute exacerbations in asthma ("yellow zone") is not clear. While some studies have suggested efficacy of increasing ICS doses acutely, a recent Cochrane review found that doubling the dose was insufficient to preventing asthma exacerbations. The multicenter STICS trial found no difference in asthma exacerbations requiring systemic steroids, reduced symptoms or albuterol during exacerbations, or treatment failure in asthmatic children assigned to high- versus low-dose ICS. Children treated with high-dose ICS tended to have slower growth. The results indicate that increasing ICS, even to five times the dose, fails to prevent pediatric asthma exacerbations.

D.A.K.

Jackson DJ, Bacharier LB, Mauger DT, et al: Quintupling inhaled corticosteroids to prevent childhood asthma exacerbations.
N Engl J Med. 2018;378:891-901.

Keywords: asthma (child), exacerbations, inhaled corticosteroids

High-Dose ICS for Exacerbations: Questionable Benefit in Adult Asthma

Acute exacerbations are common, costly, and occasionally fatal in adults with asthma. As part of an asthma self-management plan, some guidelines have suggested increasing the dose of inhaled corticosteroids (ICS) during periods of deteriorating asthma control. This UK trial evaluated the efficacy of quadrupling the dose of ICS to prevent exacerbations in adult asthma.

The open-label pragmatic trial included 1,871 asthmatic patients, aged 16 or older, who had at least one exacerbation requiring systemic glucocorticoids in the previous year. Patients were randomly assigned to one of two "zone 2" asthma self-management plans: one group was instructed to quadruple their ICS dose during periods of deteriorating asthma control, while the other group was instructed to maintain their usual ICS dose.

Quadrupling the ICS dose led to a significant reduction in the primary outcome, time to first severe asthma exacerbation: adjust-

ed hazard ratio 0.81. Number needed to treat to prevent one severe asthma exacerbation was 15. The quadrupling group was also more likely to start systemic glucocorticoids during the study period: 33% versus 40%, incidence rate ratio 0.82. Quadruple ICS dosing also led to a higher rate of treatment-related adverse events, including oral candidiasis treated with topical antifungals.

A self-management program including quadrupling the ICS dose in zone 2 may reduce severe exacerbations in adolescents and adults with asthma. Although significant, the magnitude of the reduction in exacerbation rate was smaller than expected. Given the potential toxicity of ICS and the limitations of the study design, the authors question whether the treatment effect is clinically meaningful.

COMMENT: This study evaluated quadrupling the ICS dose in asthma patients aged 16 or older as a self-management plan. Severe exacerbations occurred in 45% of patients assigned to quadruple their ICS dose, compared to 52% in the non-quadrupling group: a statistically significant difference. The median ICS dose for quadrupling was 3.2 mg of beclomethasone for 7 to 14 days, which could have had the same effect as systemic steroids. There were five times as many reports of oral candidiasis in the quadrupling group. While this study reports a "positive" effect, the clinical relevance is doubtful, given the small effect size, very high doses used, and high adverse effects. I think the study indicates that this strategy is not very effective in adults, as in the companion article in children.

D.A.K.

McKeever T, Mortimer K, Wilson A, et al: Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. N Engl J Med. 2018;378:902-910.

Keywords: asthma (adult), exacerbations, inhaled corticosteroids

Meta-Analysis Supports SMART for Persistent Asthma

Current FDA-approved treatment for persistent asthma consists of inhaled corticosteroids (ICS) and long-acting β-agonists (LABA) used as daily controller therapies, with short-acting β-agonists (SABAs) as needed for symptom relief. Some have advocated using ICS and formoterol as needed instead of SABAs, with the goal of providing immediate symptom relief while delivering ICS sooner. The authors performed a meta-analysis of the evidence on this "single maintenance and reliever therapy" (SMART) approach.

A systematic review identified 16 randomized trials evaluating SMART for persistent asthma, compared to ICS with or without LABA as controller therapy and SABA as reliever therapy. The studies included a total of 22,748 patients; in all but 1 trial, SMART consisted of budesonide plus formoterol in a dry-powder inhaler.

In 22,524 adults aged 12 or older (mean 42 years), SMART was associated with significant reduction in asthma exacerbations, compared to the same dose of ICS combined with LABA: risk ratio (RR) 0.68, with a risk difference (RD) of –2.8%. Studies comprising SMART with ICS alone as controller therapy showed a similar effect: RR 0.59, RD –11.0%.

Analysis of children aged 4 to 11 included 341 patients, median 8 years. The data suggested significant reduction in exacerbation risk with SMART, compared to the same dose of ICS plus LABA (RR 0.38, RD –23.2%) or ICS alone as controller therapy (RR 0.55, RD –12.0%). In both age groups, neither symptoms nor FEV_1 were significantly improved with SMART.

Available evidence shows that the SMART approach reduces exacerbation rate in persistent asthma, compared to controller therapy with ICS plus LABA or ICS alone. Data in childhood asthma are limited. Further studies are needed to confirm the efficacy of SMART, including other outcomes such as asthma control and quality of life.

COMMENT: Single-inhaler therapy, or single maintenance and reliever therapy (SMART), is recommended for asthma management in the GINA guidelines. Currently, the SMART protocol is not approved by the FDA. Sobieraj and colleagues performed a meta-analysis of patients with persistent asthma, comparing SMART with ICS as controller therapy (with or without a LABA) and SABAs as reliever therapy. The SMART approach was associated with a lower risk of asthma exacerbations, with a nonsignificant trend toward improvement in lung function.

J.J.O.

Sobieraj DM, Weeda ER, Nguyen E, et al: Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. JAMA. 2018;319:1485-1496.

Keywords: asthma (adult), asthma (child), exacerbations, SMART

FOCUS ON CORTICOSTEROID RISKS

Harms Associated with Oral Corticosteroid Bursts

For patients with severe or uncontrolled asthma, continuous exposure to oral corticosteroids (OCS) is associated with potentially severe adverse events. Less is known about the harms associated with intermittent OCS treatment. This study examined the association between number of OCS prescriptions and adverse events in adult asthma patients.

The retrospective analysis used data on asthmatic patients aged 18 or older from an insurance claims database between 2000 and 2014. Propensity score matching identified cohorts of 72,063 patients treated with OCS and 156,373 who did not receive OCS. Number of OCS prescriptions was analyzed for association with new incident adverse events, with follow-up of 2 to 12 years.

Patients receiving 4 or more OCS prescriptions were more likely to experience a new adverse event: odds ratio (OR) 1.29. For those with 1 to 3 prescriptions, the OR was

1.04. For each year of exposure to 4 or more OCS prescriptions, the OR for experiencing an adverse event in the current year was 1.20. For 1 to 3 prescriptions in previous years, the OR was 1.07. For 4 or more OCS prescriptions, associated ORs were 1.44 for osteoporosis, 1.33 for gastrointestinal ulcer/bleeding, 1.32 for hypertension, 1.30 for type 2 diabetes, 1.28 for obesity, 1.26 for cataracts, and 1.21 for fractures.

For asthma patients with intermittent OCS exposure, each successive prescription may be associated with increased risk of adverse events. The impact on current and future health may occur regardless of dose and treatment duration. The investigators conclude, "OCS-sparing strategies are extremely important to improve patient outcomes."

COMMENT: Patients with severe persistent asthma continuously treated with OCS are candidates for intervention to eliminate corticosteroid dependency. This retrospective cohort study provides evidence to extend this recommendation to asthma patients with intermittent exposure via OCS bursts. This also is a population with poorly controlled persistent asthma who are at risk for untoward health care outcomes from corticosteroid reliance—about which, according to these data, we should not be complacent.

D.M.L.

Sullivan PW, Ghushchyan VH, Globe G, Schatz M: Oral corticosteroid exposure and adverse effects in asthmatic patients.

J Allergy Clin Immunol. 2018;141:110-116.

Keywords: adverse events, asthma (adult), asthma (severe), oral corticosteroids

No Association Between ICS and Fractures in Children with Asthma

There is concern that daily use of inhaled corticosteroids (ICS) by children with asthma could lead to an increased risk of fractures. This risk was assessed in a large population of asthmatic children.

Using data from the Ontario Drug Benefit Program, the researchers identified 3,884 asthmatic children with any type of fracture. These cases were matched for date of birth, sex, and age at diagnosis to 15,536 asthmatic controls. Use of ICS was assessed in a 1-year lookback period. Fracture risk was compared for children with no ICS use versus current use (prescription filled within 90 days), recent use (within 91 to 180 days), or past use (181 to 365 days).

Sixty-one percent of children were male; nearly one-third were 6 to 9 years old at their index date. In multivariable conditional logistic regression analyses, fracture risk was unrelated to ICS use—current, recent, or past—compared to no ICS use. The results were unchanged in additional analyses, including treating ICS use as a binary variable. In contrast, systemic corticosteroid use was significantly associated with fractures: odds ratio (OR) 1.17 for filling one prescription. This effect was larger in girls: OR 1.25.

In children with asthma, prescription and use of ICS is not associated with increased fracture risk. Systemic corticosteroids are linked to an increased risk of fractures. The authors conclude that fracture risk is not a reason to limit use of ICS, which may in fact decrease the risk of exacerbations requiring systemic corticosteroids.

COMMENT: In addition to concern about growth impact of ICS in asthmatic children, there are worries about bone density and potential increased risk for fracture. This case-control study used Ontario pharmacy databases to evaluate the risk of bone fracture associated with ICS in more than 391,000 children with asthma. There were only 3,884 cases with fracture, with no increased risk for fracture in children treated with ICS. Children treated with systemic corticosteroids did have an increased risk for fracture. The data showed problems with adherence, since only 50% of the children regularly filled their ICS prescription. Once again, this study reinforces the importance and safety of ICS for asthma control.

S.M.F.

Gray N, Howard A, Zhu J, et al: Association between inhaled corticosteroid use and bone fracture in children with asthma.

JAMA Pediatr. 2018;172:57-64.

Keywords: asthma (child), bone effects, ICS

More to Learn About Mepolizumab in Severe Eosinophilic Asthma

Anti-interleukin 5 (IL-5) therapy with mepolizumab, given in a 100 mg sc fixed dose, is approved for treatment of eosinophilic asthma. However, this treatment has only modest benefits in prednisone-dependent patients with uncontrolled eosinophilia. This study assessed the benefits of reslizumab, administered IV in a weight-adjusted dosing regimen, in patients previously treated with fixed-dose mepolizumab.

The study included 10 prednisone-dependent asthma patients with eosinophilia, defined as a sputum eosinophil percentage greater than 3% and blood eosinophil count greater than 300 cells/μL. As part of an open-label trial, all had received at least 1 year of treatment with mepolizumab, 100 mg sc every 4 weeks. After a 12-month washout period and 2-month placebo period, all patients received reslizumab, 3 mg/kg IV every 4 weeks for 4 months. Sputum and blood responses to reslizumab were evaluated along with secondary outcomes.

Mean reslizumab dose was 254.3 mg. Reslizumab therapy led to a 91.2% reduction in sputum eosinophils, an 87.4% reduction in blood eosinophil count, and a 65.5% reduction in sputum eosinophil peroxidase level. The reductions in eosinophilia were associated with improvements in FEV_1 and asthma control questionnaire scores. The decrease in sputum eosinophil percentage was greater with reslizumab compared to mepolizumab (42.7% versus 5.0%), associated with a larger improvement in asthma control questionnaire score. Sputum IL-5 and anti-eosinophil peroxidase IgG were predictors of response to anti-IL-5 therapy.

In patients with prednisone-dependent severe asthma, weight-adjusted intravenous reslizumab provides better reduction in airway eosinophilia than fixed-dose subcutaneous mepolizumab. The reductions in airway eosinophilia are associated with better asthma control. Higher concentrations of anti-IL-5 monoclonal antibody in the airway may be needed to neutralize local IL-5 levels.

Anti-IL-5 therapy with mepolizumab reduces circulating eosinophils and the frequency and severity of exacerbations in patients with severe, eosinophilic asthma. Little is known about the functional phenotype of eosinophils that remain in the airway and blood after IL-5 therapy. This experimental study assessed changes in eosinophil numbers and phenotypes in response to a single dose of mepolizumab.

The study included 10 patients with mild, reversible allergic asthma. These subjects underwent segmental allergen challenge, performed before and 1 month after administration of one 750 mg IV dose of mepolizumab. Changes in eosinophil numbers and phenotypes in blood, bronchoalveolar lavage, and endobronchial biopsy specimens were assessed 48 hours after allergen challenge.

Before mepolizumab, allergen challenge produced increases in circulating eosinophil count, eosinophilia in bronchoalveolar lavage, and eosinophil peroxidase deposition in bronchial mucosa. After IL-5 monoclonal antibody, the allergen-induced increases in circulating eosinophils and IL-3 receptor expression were eliminated, while airway eosinophilia and eosinophil peroxidase deposition were reduced. Allergen challenge also induced an activated phenotype of bronchoalveolar lavage eosinophil surface markers, before and after treatment with mepolizumab.

This study in mild allergic asthma patients shows reduction in airway eosinophil numbers induced by allergen after administration of mepolizumab. However, patterns of airway eosinophil activation markers are little changed by anti-IL-5 monoclonal antibody, which may help to explain why mepolizumab therapy reduces but does not eliminate asthma exacerbations.

COMMENT: These two articles give us some insight into the mechanism of action of mepolizumab and the possible reason for nonresponse to therapy. In the proof-of-concept study from the McMaster group, weight-based dosing of IV reslizumab caused greater improvement in asthma control in prednisone-dependent patients with eosinophilic asthma who had not responded to fixed-dose mepolizumab.

The second study investigates the mechanism of action of the eosinophil-lowering dose of mepolizumab in an experimental allergen challenge model. Although mepolizumab reduced airway eosinophil numbers, it did not affect functional status. The accompanying editorial by Papi et al (Am J Respir Crit Care Med 2018;197:1-2) reinforces this point.

B.E.C.

Mukherjee M, Paramo FA, Kjarsgaard M, et al: Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. Am J Respir Crit Care Med. 2018;197:38-46.

Kelly EA, Esnault S, Liu LY, et al: Mepolizumab attenuates airway eosinophil numbers, but not their functional phenotype, in asthma. Am J Respir Crit Care Med. 2017;196:1385-1395.

Keywords: anti-IL-5 therapy, asthma (adult), asthma (severe), eosinophilic asthma

Omalizumab Lowers Susceptibility to Rhinovirus Infection

Patients with allergic sensitization are clearly more susceptible to respiratory viral illness, particularly caused by rhinovirus (RV). However, it is unclear whether this is a causal association. In the "Preventative Omalizumab or Step-up Therapy for Fall Exacerbations" (PROSE) study, preseasonal omalizumab treatment reduced viral-induced asthma exacerbations in children. The PROSE data were analyzed to assess omalizumab's effects on RV illness in children with allergic asthma.

The study included 478 children from low-income areas in eight US cities. Weekly virology findings were analyzed for 89 children assigned to guideline-based asthma therapy and 259 receiving add-on omalizumab, and compared for the presence of RV. Respiratory symptoms and asthma exacerbations were assessed during a 90-day period in the fall season.

Rhinovirus was more than twice as likely to be detected in nasal mucus samples obtained during exacerbations compared to nonexacerbation samples: 57% versus 36% of samples, odds ratio (OR) 2.32. Associations with asthma exacerbation were strongest for rhinovirus C (OR 2.85) and A (OR 2.92), but were also significant for rhinovirus B (OR 1.98). Omalizumab was associated with a 1-day reduction in duration of RV infection, 11.2 versus 12.4 days; and with a 0.4-log unit reduction in peak RV shedding. The frequency of RV illness was one-third lower in children treated with omalizumab: risk ratio 0.64.

In children with allergic asthma, omalizumab is associated with reduced RV infection and associated illness. Children receiving preseasonal omalizumab also have fewer viral asthma exacerbations and reduced duration and peak of viral shedding. Reducing IgE may limit RV replication and promote clearance, thus reducing the frequency and severity of upper and lower respiratory viral illness.

COMMENT: This reanalysis of the PROSE Trial shows us that the preseasonal use of omalizumab can decrease the length and severity of respiratory infections due to RV. This is especially helpful in patients with a recent history of asthma attacks. The findings help us to better understand the biology of interferon production associated with RV infections, which helps to attenuate viral shedding and decrease the frequency of respiratory viral illnesses. See accompanying editorial by Saglani and Bush (Am J Respir Crit Care. 2017;196:941-942).

B.E.C.

Esquivel A, Busse WW, Calatroni A, et al: Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma.

Am J Respir Crit Care Med. 2017;196(8):985-992.

Keywords: (asthma) child, exacerbations, omalizumab, rhinovirus

Omalizumab and the Eosinophilic Phenotype

Clinical and biologic markers of asthma severity may help to identify patients more likely to respond to omalizumab and other biologic therapies. Higher blood eosinophil counts, suggesting an underlying Th2 phenotype, have been linked to more severe asthma and a higher risk of exacerbations. Data from pivotal trials of omalizumab were analyzed to assess baseline blood eosinophil count as a predictor of response.

The analysis included 1,071 adolescent or adult patients with allergic asthma who were randomly assigned to treatment with omalizumab or placebo. Low and high baseline blood eosinophil counts (with a cutoff point of 300 μL) and several asthma severity markers were analyzed as predictors of a better response to omalizumab. The primary endpoint was the rate of exacerbations during a 16-week period on a stable dose of inhaled corticosteroid.

Rates of exacerbations requiring 3 or more days of systemic corticosteroid therapy were 6.66% in omalizumab-treated patients versus 14.7% in the placebo group, for a relative rate reduction of 55%. By level of baseline blood eosinophil count, the relative rate reductions were 55% at 200 μL or higher, 67% at 300 μL or higher, and 74% at 400 μL or higher. Markers of more severe asthma were also associated with a larger response to omalizumab.

Allergic asthma patients with high blood eosinophil counts or markers of severe asthma have a greater reduction in exacerbations in response to omalizumab. The benefit of omalizumab is seen across a wide range of eosinophil levels, rather than a specific cutoff point. The authors note that omalizumab trials might have reported a larger effect, had they enrolled a more enriched patient population.

COMMENT: Post-hoc analysis of pooled data from two pivotal trials found that the reduction in exacerbation rates in patients assigned to omalizumab was more pronounced in association with higher baseline levels of peripheral eosinophils. This finding is consistent with other studies, which demonstrate that high baseline eosinophil counts identify an exacerbation-prone subgroup more likely to experience clinically meaningful improvement of poorly controlled asthma with administration of biologic agents.

D.M.L.

Casale TB, Chipps BE, Rosén K, et al: Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma.

Allergy. 2018;4:941-947.

Keywords: asthma (adult), biologics, eosinophilic asthma, omalizumab

Oral Corticosteroids for Viral Asthma Exacerbations in Preschoolers

Virus-associated wheezing is common in preschool-aged children. Corticosteroids reduce the need for hospitalization in adults with asthma, but studies of their use in pediatric wheeze exacerbations have yielded conflicting results. This trial evaluated the efficacy of oral prednisolone in preschool-aged children seen in a pediatric emergency department (ED) for virus-associated wheeze.

The randomized controlled trial included 624 children, aged 24 to 72 months, seen in an Australian pediatric ED for suspected virus-associated wheeze. Patients were assigned to double-blind treatment with oral prednisolone, 1 mg/kg/d, or placebo for 3 days. Total length of stay until hospital discharge was compared between groups. After an initial non-inferiority analysis, a post-hoc superiority analysis was performed.

A modified intention-to-treat analysis included 605 children: approximately two-thirds male, median age about 41 months. Oral prednisolone was associated with a shorter length of stay until readiness for discharge—540 versus 370 minutes—and was superior to placebo. Unadjusted ratio of geometric mean for length of stay was 0.79 for prednisolone relative to placebo. There were no serious adverse events in either group.

The clinical trial shows a "clear benefit" of oral prednisolone for preschool-aged children seen in the ED for virus-associated wheezing. The impact on length of stay is greatest in children with severe features of wheeze, previous treatment with albuterol, and history of asthma. Past or family history of atopy did not predict a response to prednisolone.

COMMENT: This study explores the utility of oral corticosteroids (OCS) in preschool children with virus-associated wheeze presenting to the pediatric ED. Although OCS has demonstrated efficacy in adults and adolescents with viral-induced wheeze, studies in preschoolers have reported contradictory findings. On post hoc analysis of a randomized trial, OCS had a clear benefit in reducing the length of stay of children seen in the ED with virus-associated wheeze. In the accompanying editorial (Lancet Respir Med. 2018;6:76-77), Zorc notes that although there is only a 170-minute change in median length of stay, steroids take several hours to reach maximal effect—and thus timely steroid treatment could translate to reduced hospitalizations.

J.J.O.

Foster SJ, Cooper MN, Oosterhof S, Borland ML: Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomized, double-blind, placebo-controlled trial.

Lancet Respir Med. 2018;6:97-106.

Keywords: asthma (child), emergency department, oral corticosteroid, viral infections

Tiotropium May Prevent Asthma Exacerbations in Children

There is little evidence to guide treatment for asthma in children under age 5 whose disease is not well-controlled with low-dose inhaled corticosteroid (ICS). Once-daily tiotropium via the Respimat inhaler has proved to be a well-tolerated and effective add-on therapy in adults, adolescents, and school-aged children with asthma. This study explored the use of tiotropium in 1- to 5-year-old children with persistent asthma symptoms.

The randomized trial included 102 children, enrolled at 32 centers in 11 countries, with asthma symptoms that had persisted for at least 6 months despite ICS. Patients were randomly assigned to double-blind treatment with tiotropium via Respimat inhaler, 2.5 or 5.0 μg once daily, or placebo. These treatments were added on to ICS, with or without additional controller therapy. The main efficacy outcome was change in weekly mean combined daytime asthma symptom score.

The analysis included 101 children who completed 12 weeks of treatment. Change in adjusted weekly symptom score was not significantly different between groups, with differences of –0.080 with tiotropium 2.5 μg and –0.048 with tiotropium 5.0 μg (versus placebo).

On safety analysis, adverse events occurred in 56% of children with tiotropium 2.5 μg and 58% with the 5.0 μg dose, compared to 74% of the placebo group. Rates of asthma exacerbations as adverse events were 14% and 6% in the tiotropium groups, respectively, compared to 29% with placebo. Three children, all in the placebo group, had serious adverse events requiring hospitalization.

Add-on therapy with tiotropium does not reduce daytime symptom scores in 1- to 5-year-old children with persistent asthma. However, both study doses of tiotropium appear to reduce the risk of asthma exacerbations in these young children. The authors call for further trials to evaluate this potential complementary treatment strategy.

COMMENT: This multinational exploratory phase 2/3 regulatory trial examined the efficacy and safety of adding tiotropium (2.5 and 5 μg) versus placebo in 1- to 5-year-olds who were symptomatic despite use of ICS. The primary endpoint of mean daytime asthma symptom scores was not significantly different between groups. However, tiotropium demonstrated the potential to reduce asthma exacerbations compared to placebo, with no added safety issues. This finding is quite impressive, considering the small sample size (only 68 subjects in total receiving tiotropium) and descriptive statistical analysis. As noted by the authors, additional, well-powered trials are needed to further assess the utility of add-on tiotropium in young children.

J.J.O.

Vrijlandt EJLE, El Azzi G, Vandewalker M, et al: Safety and efficacy of tiotropium in children aged 1- 5 years with persistent asthmatic symptoms: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2018;6:127-137.

Keywords: add-on therapy, asthma (child), persistent asthma, tiotropium

Vitamin D Is Not Effective for Primary Allergy Prevention

Previous studies have suggested that low vitamin D levels may be associated with an increased risk of developing allergic diseases. The authors present the first systematic review of evidence on the safety and efficacy of vitamin D supplementation for primary prevention of allergies.

A comprehensive literature review identified five studies of vitamin D versus no supplementation for primary prevention of allergic diseases in pregnant or breast-feeding women, infants, or children. The sole randomized trial, evaluating vitamin D supplementation during pregnancy, found no effect of vitamin D for any allergy outcome in offspring: atopic dermatitis, asthma or wheezing, allergic rhinitis, or food allergy.

The other four studies were case-control or cohort studies evaluating vitamin D supplementation in pregnant women and infants, in breast-feeding women, or in infants. The data showed no effect on allergy or allergic disease outcomes. There were no eligible studies of vitamin D for primary prevention of allergic diseases in children.

The systematic review finds "very low certainty" in available studies of vitamin D supplementation for primary prevention of allergic disease in pregnant or breast-feeding women, or in infants or children. Along with other studies—including recent randomized trials comparing high- versus low-dose vitamin D—the findings do not support recommendations for vitamin D supplementation to prevent allergies.

COMMENT: A previous umbrella review (Theodoratou E, et al: BMJ. 2014;348:g2035) identified 107 systematic reviews and 74 meta-analyses of observational studies of vitamin D concentrations and 87 meta-analyses of RCTs of vitamin D supplementation, for 137 outcomes covering multiple disorders. The reviewers concluded: "highly convincing evidence of a clear role of vitamin D does not exist for any outcome." They found three "probable" outcomes: dental caries in children, low birth weight, and parathyroid hormone levels in renal failure patients on dialysis. The present systematic review implies that we should not be recommending vitamin D as an intervention for primary prevention of allergic disorders.

D.M.L.

Yepes-Nuñez JJ, Brożek JL, Fiocchi A, et al: Vitamin D supplementation in primary allergy prevention: systematic review of randomized and non-randomized studies. Allergy. 2018;73:37-49.

Keywords: allergic disease, prevention, vitamin D

Prenatal Tobacco Exposure May Be Worse Than Postnatal Exposure

Tobacco smoke exposure (TSE) has been linked to airflow obstruction in young children. Because many children have TSE during both the prenatal and postnatal period, it is difficult to determine which exposure period is more harmful. This study assessed the relationship between current TSE and airflow obstruction in children, with adjustment for prenatal TSE.

The study included 2,070 children, aged 6 to 11, who participated in the National Health and Nutrition Examination Survey (NHANES) during 2007-12 and had available data on serum cotinine levels and spirometry results. Airflow obstruction, defined as a prebronchodilator FEV_1/FVC ratio below the 5th percentile of the lower limit of normal, was present in 9.6% of children.

Initial analysis suggested that cotinine levels were associated with airflow obstruction: odds ratio (OR) 1.12. However, the association was no longer significant on multivariate analysis including both cotinine and self-reported prenatal TSE as covariates. Cotinine was unassociated with airflow obstruction in both asthmatic and nonasthmatic children. Prenatal TSE was associated with airflow obstruction in children with asthma—adjusted OR 2.51—but not in nonasthmatic children.

The population-based data show no independent relationship between postnatal TSE, as measured by cotinine, and airflow obstruction in children. Reported prenatal TSE is associated with airflow obstruction, but only in children with asthma. The results suggest that the effect of TSE may be strongest during fetal development. Prenatal TSE "may define a phenotype who develop asthma as a result of relatively smaller airways," the authors conclude.

COMMENT: Tobacco smoke exposure is associated with increased respiratory symptoms and asthma in children. This study evaluated NHANES data including spirometry and urinary cotinine levels. Tobacco exposure during pregnancy was associated with airflow obstruction, but mainly in asthmatic children. Interestingly, postnatal TSE was not associated with airflow limitation. Perhaps the best time to quit smoking is during pregnancy.

D.A.K.

Brown S-AW, Liu B, Taioli E, et al: The relationship between tobacco smoke exposure and airflow obstruction in US children: analysis of the National Health and Nutrition Examination Survey (2007-2012).
Chest. 2018;153:630-637.

Keywords: airflow obstruction, asthma (child), smoking

Does Smoking Prevent AERD?

Patients with aspirin-exacerbated respiratory disease (AERD) have low expression of cyclo-oxygenase-2 (COX-2) in airway epithelia, leading to decreased production of prostaglandin E_2 (PGE_2). Cigarette smoking increases COX-2 expression, which might increase PGE_2 levels and thus protect against AERD. This study evaluated whether smoking cessation leads to increased risk of AERD.

The study included 114 patients with AERD; two groups of patients with aspirin-tolerant asthma (ATA), 83 diagnosed by systemic aspirin provocation test (ATA-1) and 914 from a Japanese database (ATA-2); and 2,313 healthy controls. Associations between smoking and the development of AERD were assessed.

At the age of asthma onset, 9.7% of AERD patients were current smokers, compared to 20.5% in the ATA-1 group, 24.5% in the ATA-2 group, and 26.2% in the healthy control group. In contrast, 20.2% of AERD patients were past smokers, compared to 12.0% of ATA-1, 10.3% of ATA-2, and 12.6% of healthy controls. With adjustment for confounders, quitting smoking within the past 1 to 4 years was positively associated with AERD risk: odds ratio 4.63 compared to the ATA-2 group and 4.09 for the healthy control group.

The findings support the hypothesis that smoking cessation may increase the risk of developing AERD. The authors emphasize the need for further studies, including the effect of PGE_2, on the relationship between smoking and AERD.

COMMENT: Cigarette smoking appears to upregulate an array of inflammatory mediators and cytokines, including COX-2 expression and PGE_2 production, both locally in the airway epithelia and systemically. In addition, smoking increases EP2 receptor expression in lung fibroblasts, neutrophils, and alveolar macrophages. The authors suggest that the resultant inflammatory milieu may prevent the development of AERD. On the other hand, with smoking cessation, there is a reduction in PGE_2 production and EP2 receptor expression, which might induce the development of AERD. Certainly, this study indicates that the cessation of cigarette smoking may be a risk factor for the development of AERD. Further clinical and mechanistic studies are needed to better understand the effect of smoking exposure on the pathogenesis of AERD. In the meantime, I would still encourage smoking asthmatics to discontinue their habit.

J.J.O.

Hayashi H, Fukutomi Y, Mitsui C, et al: Smoking cessation as a possible risk factor for the development of aspirin-exacerbated respiratory disease in smokers.
J Allergy Clin Immunol Pract. 2018;6:116-125.

Keywords: AERD, smoking

Can T Cells Help Define Food Allergy in EoE?

In patients with eosinophilic esophagitis (EoE), inflammation triggered by food allergens may lead to esophageal dysfunction and fibrosis. Esophageal biopsies show eosinophilia with Th2 cytokine expression. The investigators looked

for Th2 cells in peripheral blood samples from children with milk-induced EoE.

The study included 20 children with milk-induced EoE—15 males and 5 females, mean age 11.25—and 8 healthy controls. In the EoE group, peripheral blood mononuclear cells were collected when the children were consuming milk and had active EoE and again when they were not consuming milk and had inactive EoE. T-cell phenotypes were analyzed, including assessment of intracellular cytokines before and after incubation with milk antigens.

Blood samples from children with EoE had increased CD4+ Th2 cells, compared to healthy controls. During the active EoE period, there was an increase in the activation marker of CD154+ T cells: mean 0.17%, compared to 0.034% in controls. In active EoE samples, the CD4+ T cells expressed higher levels of Th2 cytokines (ie, interleukins 4, 5, and 13), compared to inactive EoE or control samples. Incubation with milk antigens increased CD3+CD4+CD154+IL-5+ T cells in both active and inactive EoE samples, compared to controls.

The study demonstrates specific activation to milk allergens in peripheral blood T cells from children with milk-induced EoE. Activated T cells might be a useful biomarker for EoE, enabling a serum-based test that could be used to assess disease activity and identify the food allergens involved.

COMMENT: Another exciting study for patients with eosinophilic esophagitis. These children with EoE that resolved after removal of milk from their diets—despite negative milk-specific IgE testing—remind us that our patient testing with current laboratory exams is not ideal. The authors found increased milk-specific Th2 lymphocytes in the peripheral blood of their patients. This study may have important clinical implications for several reasons. Since it can be difficult to identify foods involved in EoE by specific IgE testing, the prospect of having a relatively noninvasive test gives patients hope regarding possible monitoring of their disease activity. Further studies could also look at measuring specific Th2 lymphocytes to other foods or whether this is seen in other forms of atopic disease.

V.H.-T.

Cianferoni A, Ruffner MA, Guzek R, et al: Elevated expression of activated T_H2 cells and milk-specific T_H2 cells in milk-induced eosinophilic esophagitis.
Ann Allergy Asthma Immunol. 2018;120:177-183.

Keywords: EoE, food allergy

Pediatric EoE: Prenatal, Intrapartum and Postnatal Factors

Early-life exposures might contribute to the rising prevalence of eosinophilic esophagitis (EoE). Data from a children's hospital registry were used to examine prenatal, intrapartum, and postnatal risk factors for pediatric EoE.

The study included the mothers of 127 children with diagnosed EoE, mean age 10.6 years, and 121 controls. Identified from a study of genetic risk factors for EoE, all subjects were non-Hispanic white. Males accounted for 80.3% of EoE cases; 83.3% had food allergies, 59.1% had eczema, and 44.9% had asthma.

Prenatal factors associated with EoE included maternal fever, adjusted odds ratio (OR) 3.18, and preterm labor, OR 2.18. Cesarean delivery was a significant intrapartum factor: OR 1.77. Postnatal factors associated with development of EoE were treatment with antibiotics or acid suppressants during pregnancy: OR 2.30 and 6.05, respectively. The presence of a dog or cat at home during infancy was inversely associated with EoE: OR 0.58. There was no protective effect of breastfeeding or maternal multivitamin or folic acid supplement use.

The study is the largest so far to look at early-life factors associated with the development of EoE in children. In addition to providing insights into pathogenesis, the study identified potentially modifiable risk factors that might have implications for prevention of EoE.

COMMENT: The incidence of EoE has been increasing in recent years. This relatively large, case-controlled study from Cincinnati analyzed various early-life influences associated with EoE. Certain associations known to impact atopy such as pet exposure were protective, but maternal fever, preterm labor, cesarean section, and early use of antibiotics or acid suppressants increased the risk for EoE. Interestingly, breastfeeding and use of prenatal supplements or vitamins were not protective. The authors suggest that by identifying modifiable factors one could potentially alter the development of EoE.

S.M.F.

Jensen ET, Kuhl JT, Martin LJ, et al: Prenatal, intrapartum and postnatal factors are associated with pediatric EoE.
J Allergy Clin Immunol. 2018; 141: 214-222.

Keywords: EoE, risk factors

Targeting Eosinophils in COPD

Anti-interleukin-5 therapy with mepolizumab reduces exacerbations and improves other outcomes in severe eosinophilic asthma. A pair of phase 3, randomized, double-blind, placebo-controlled trials evaluated the benefits of mepolizumab in patients with chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype.

Both trials included patients with COPD who had a history of moderate or severe exacerbations while receiving inhaled glucocorticoid-based triple maintenance therapy. In the "Mepolizumab vs Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients" (METREX) study, unselected patents were stratified according to blood eosinophil count (150/mm^3 or higher at screening or 300/mm^3 or higher during the previous year), then assigned to mepolizumab 100 mg sc every 4 weeks for 1 year or

placebo. In a modified intention-to-treat analysis including 462 patients, mepolizumab reduced the rate of moderate to severe exacerbations only among patients with an eosinophilic phenotype: 1.40 versus 1.71 per year, adjusted rate ratio 0.82. There was no significant difference in the overall modified intention-to-treat population.

In the "Mepolizumab vs Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level" (METREO) study, all patients had an eosinophilic phenotype. Exacerbation rate was reduced with both a 100 or 300 mg dose of mepolizumab versus placebo: rate ratio 0.80 and 0.86, respectively. The effect on exacerbation rate was greater in patients with a higher screening blood eosinophil count.

These trials support the efficacy of mepolizumab in reducing exacerbations for patients with COPD and an eosinophilic phenotype. The extent of benefit is greater in patients with a higher blood eosinophil count. The results "show the importance of blood eosinophils in COPD exacerbations," the researchers note.

COMMENT: While we know that eosinophils play an important role in asthma, their role in COPD has not been recognized. Recent research has shown that airway eosinophilia is present in up to 40% of individuals with COPD and is associated with an increased risk of exacerbations, even in those without asthma. This was further demonstrated in two 12-month trials of mepolizumab in the treatment of COPD. The METREX study found a significant difference in annual exacerbation rate when subjects were stratified according to eosinophil count. The METREO study showed a trend toward a greater effect of mepolizumab among patients with higher blood eosinophil counts at screening. These studies highlight the need to understand better the role of eosinophils and other biomarkers in the evolution and management of individuals with COPD. See the accompanying editorial by McDonald: N Engl J Med. 2017:377:1680-1682.

C.D.

Pavord ID, et al: Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med. 2017;377:1613-1629.

Keywords: biologics, COPD, eosinophils, mepolizumab

Microscopic Emphysema in Asthma with Normal CT scans

Previous studies have described reversible loss of elastic lung recoil and hyperinflation at total lung capacity during acute attacks in patients with chronic, persistent asthma who have never smoked. In an autopsy study, the authors reported four such cases with unsuspected mild, diffuse, centrilobular asthma in the upper and middle lung. They report a fifth case, along with further studies in never-smoking asthma patients with persistent expiratory obstruction.

The patients were 13 men and 12 women, mean age 55 years, with stable asthma of variable type 2 phenotype. After administration of 270 μg of aerosolized albuterol sulfate via spacer chamber, the patients had a mean FVC of 3.1 L (83% of predicted), FEV_1 of 1.8 L (59% of predicted), and FEV_1/FVC ratio of 59% ± 10%, with a ratio of single-breath diffusing capacity of the lung for carbon monoxide to alveolar volume of 4.8 mL/min/mm Hg/L (120% of predicted). In all cases, loss of static lung elastic recoil pressure, together with decreased intrinsic airway conductance, led to limited expiratory airflow. Lung computed tomography scans showed little or only mild emphysema. Eight patients studied during asthma remission showed increased lung elastic recoil accompanied by increased expiratory airflow.

The authors also report a new case of unsuspected mild, diffuse centrilobular emphysema in the upper and middle lung fields in an explanted lung from a patient who underwent single-lung transplantation. Asthmatic airway remodeling was also present.

Mild emphysema may occur as a clinically unsuspected complication in patients with treated asthma who have never smoked but develop persistent expiratory airflow limitation. The presence of centrilobular emphysema is masked by normal diffusing capacity, with normal or near-normal findings on high-resolution CT scans. The authors suggest that a "proinflammatory, proteolytic cascade" may be the cause of asthma-related lung tissue breakdown and mild emphysema.

COMMENT: Nonsmoking patients with asthma who have fixed obstruction remain a puzzle. This study extends previous work by the authors, showing that such patients have loss of lung elastic recoil. In selected pathologic specimens, mild centrilobular emphysema can be seen despite normal or near-normal high-resolution CT scans. While the authors propose this is due to a proinflammatory proteolytic cascade, the prevention and management steps for these patients remains unclear.

D.A.K.

Geld AF, Yamamoto A, Verbeken EK, et al: Further studies of unsuspected emphysema in nonsmoking patients with asthma with persistent expiratory airflow obstruction. Chest. 2018;153:618-629.

Keywords: airflow obstruction, asthma (adult), emphysema

Basophil Biomarker Effects of Omalizumab in Chronic Urticaria

Omalizumab is approved for the treatment of chronic urticaria (CU), but its mechanism of action remains unclear. One proposed mechanism is reduction of FcεRI receptor density on basophils and mast cells. This trial evaluated basophil effects of omalizumab in patients with antihistamine-resistant CU.

The double-blind trial included 30 patients with symptoms of CU that did not respond to standard doses of H1-antihistamines. Patients were randomly assigned to receive • • •

four monthly doses of omalizumab, 300 mg, or placebo, with a follow-up visit two months after the last treatment.

The omalizumab-treated group had "rapid and significant" reduction in FcεRI receptor density, compared to placebo: 72.89 versus 27.83 × 10^3 receptors/basophil. This occurred within as little as 1 week and was sustained throughout the treatment period. There was no effect on basophil "releaseability" or on the basophil activation test (CU-BAT) of patient serum using donor basophils. In a post hoc analysis, the omalizumab-related reduction in FcεRI density was greater in patients classified as responders (early or slow), compared to partial/non-responders.

This randomized trial shows reduced basophil FcεRI receptor density in CU patients treated with omalizumab. The lack of effect on the CU-BAT suggests a primarily cellular effect on basophils. The investigators conclude,"To predict the omalizumab response time and to monitor disease, FcεRI density and CU-BAT might be promising cellular-based assays."

COMMENT: The mechanism for the effect of omalizumab in CU remains unclear. These investigators analyzed FcεRI expression on basophils, anti-IgE stimulation of basophils, and serum activation of pooled donor basophils (basophil activation test) in a small double-blind study of omalizumab therapy in CU. As has been shown before, FcεRI expression on basophils decreased rapidly, even in patients who did not respond to omalizumab. No significant differences were seen for other functional assays of basophils. Despite the authors' conclusions, these basophil tests do not appear to have value in evaluating responses to omalizumab in CU patients.

D.A.K.

Jörg L, Pecaric-Petkovic T, Reichenbach S, et al: Double-blind placebo-controlled trial of the effect of omalizumab on basophils in chronic urticaria patients.

Clin Exp Allergy. 2018;48:194-204.

Keywords: basophils, biologics, chronic urticaria, omalizumab

Atopic Dermatitis–Not "Just an Itch" After All

Atopic dermatitis (AD) is a common chronic inflammatory skin disease associated with increased rates of cutaneous infections. Recent reports suggest that children and adults with AD may also be at increased risk of respiratory, urinary, and other types of infections. Nationwide data were analyzed to assess the risks and outcomes of serious infections among adults with AD.

The study used data on more than 72 million adult discharges from the 2002-12 National Inpatient Sample, including a stratified sample of approximately 20% of US hospitalizations. The analysis included 9,290 admissions of patients with AD and 155,909 with eczema. Patients with AD (or eczema) were older (58.6 versus 57.0 years) and less likely to be women (55.8% versus 60.5%) than those without AD. Asthma was present in 13.7% versus 6.3% of patients, respectively.

Serious infections occurred in 42.1% of hospitalized adults with AD, compared to 25.4% of those without AD. In a multivariable model, AD was associated with 32 out of 38 infections. Adjusted odds ratios (ORs) for cutaneous infections included 67.93 for eczema herpeticum, 11.15 for erysipelas, and 4.53 for cellulitis. Other associated infections included aspergillosis, OR 1.51; tuberculosis, OR 1.57; infectious arthropathy, OR 2.01; endocarditis, OR 1.25; encephalitis, OR 1.65; and methicillin-resistant *Staphylococcus aureus,* OR 3.29. Among AD patients, hospitalization with any serious infection was associated with increased cost of inpatient care, geometric mean $8,273 versus $7,179; and increased length of stay, 5.3 versus 3.9 days (compared to AD patients without serious infection).

The data show a substantially increased risk of serious cutaneous and other infections among adults with AD. The authors estimate $11 to $228 million in excess annual costs from hospitalization with serious infections in adult AD patients. Further studies of the mechanisms and prevention of extracutaneous and systemic infections in AD are needed.

COMMENT: When someone tells you that AD is just a rash or an itch, you can tell them that research supports its association with more severe diseases. The authors report increased serious infections in hospitalized adults with AD. As we know, AD also carries a financial burden that cannot be overlooked, as well as decreased quality of life, increased length of stay, and loss of workdays due to hospitalization. The results support the need for adequate treatment of AD. We can discuss these findings with patients who may not feel the need to "treat the rash."

V.H.-T.

Narla S, Silverberg JI: Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults.

Ann Allergy Asthma Immunol. 2018;120:66-72.

Keywords: atopic dermatitis, comorbidity, infection

Is Pet Removal the Answer?

Despite the very high rate of pet ownership in the United States, the effects of exposure to pets on morbidity from asthma are unknown. This association was studied using data from the National Health and Nutrition Examination Survey (NHANES).

The analysis included data on 5,238 participants from NHANES 2005-06 with available data on home dust allergen assays and specific IgE levels in blood. Overall, 51.2% of participants owned a dog (37.9%), cat (25.7%), or both (14.3%). Rates of household pet ownership were higher in subjects with asthma: 42.2% for dogs and 31.2% for cats. Prevalence of allergic sensitization was 12.1% for dog and 12.4% for cat.

For sensitized subjects, elevated levels of pet allergen in home dust were associated with a higher prevalence

of asthma and asthmatic attacks. High exposure to pet allergen was responsible for an estimated 44.2% of asthma attacks among subjects sensitive to dog and 30.3% of those sensitive to cat. At the national level, these exposures were estimated to account for more than 1 million and more than 500,000 asthma attacks, respectively.

High numbers of asthma attacks are associated with home exposure to elevated levels of dog and cat allergen in sensitized individuals. The findings suggest that measures to reduce pet allergen exposure could substantially reduce asthma morbidity and associated costs.

COMMENT: Data from NHANES show that the combination of asthma, cat/dog exposure, and sensitivity to these pets results in excess asthma morbidity. More than 50% of the US population owns a pet and 1 in 10 children have asthma. The authors stress that efforts should be undertaken to reduce pet allergen exposure, in attempt to reduce asthma morbidity as well as healthcare utilization.

J.J.O.

Gergen PJ, Mitchell HE, Calatroni A, et al: Sensitization and exposure to pets: the effect on asthma morbidity in the US population.
J Allergy Clin Immunol. 2018;6:101-107.

Keywords: asthma (adult), asthma (child), pet allergies

In Vitro Diagnostic Tests for DRESS: Are We There Yet?

It can be difficult to identify the causative medication in patents with drug reaction with systemic symptoms (DRESS). Previous studies have reported positive results of the lymphocyte transformation test (LTT) in DRESS patients, although sensitivity and specificity have not been defined. The authors evaluated the diagnostic performance of LTT in patients with DRESS.

The study included 41 patients with DRESS diagnosed at a Spanish university hospital from 2007 to 2013. There were 26 women and 15 men, median age 61 years. The investigators performed LTT with every possible drug involved, using acute and recovery samples. Since drug rechallenge is contraindicated, the Algorithm of the Spanish Pharmacovigilance System was used for drug causality assessment.

Diagnostic performance of the LTT improved from the acute phase to the recovery phase. Sensitivity increased from 40% to 73% and specificity from 30% to 82%, respectively. Both sensitivity and specificity were better with LTT compared to skin tests. Sensitivity of the LTT was 100% for anticonvulsants, 87.5% for anti-tuberculosis drugs, and 73% for beta-lactams, with specificity of 100% for all three drug classes.

The results support the use of an LTT for diagnosis of drug causality in patients with DRESS. Sensitivity and specificity are higher in the recovery phase than in the acute phase. "This technique should at least be available in reference centres managing DRESS," the researchers write.

COMMENT: Lymphocyte transformation tests have shown promise in identifying culprit drugs in DRESS. This retrospective Spanish study evaluated a research-based LTT in the acute and recovery phases. The results showed surprisingly good specificity for beta-lactams and anti-tuberculosis drugs in the recovery phase, but not the acute phase. This study is limited by the inclusion of "possible" cases of DRESS as well as the use of a non-commercial LTT assay.

D.A.K.

Cabañas R, Calderón O, Ramírez E, et al: Sensitivity and specificity of the lymphocyte transformation test in drug reaction with eosinophilia and systemic symptoms causality assessment. Clin Exp Allergy. 2017;48:325-333.

Keywords: diagnosis, DRESS, drug hypersensitivity

REVIEWS OF NOTE

COMMENT: This is an interesting and thought-provoking review. As clinicians caring for pediatric patients, we can appreciate the questions by families regarding "How can we prevent allergy?" Although further studies are needed, the prospect of using emollients in early life to decrease atopic dermatitis is exciting. The next questions would be regarding any effect this would have on subsequent development of food allergy or asthma. This is definitely a topic to follow, as we may be able to "prevent the march."

V.H.-T.

Lowe AJ, Leung DYM, Tang MLK, et al: The skin as a target for prevention of the atopic march. Ann Allergy Asthma Immunol. 2018;120:145-151.

COMMENT: This is a wonderful review of both eosinophilic and noneosinophilic asthma, focusing on mechanisms and potential interventions.

J.J.O.

Carr TF, Zeki AA, Kraft M: Eosinophilic and noneosinophilic asthma.
Am J Respir Crit Care Med. 2018;197:22-23.

COMMENT: This review shows us that factors other than premature birth impinge upon the course of wheezing and childhood asthma.

B.E.C.

Rusconi F, Gagliardi L: Pregnancy complications and wheezing and asthma in childhood. Am J Respir Crit Care Med. 2018;197:580-588.

COMMENT: This article investigates the interaction between the microbiome and metabolic dysfunction in the early origins of asthma—an evolving area of research.

B.E.C.

Martinez FD, Guerra S: Early origins of asthma: role of microbial dysbiosis and metabolic dysfunction, Am J Respir Crit Care Med. 2018;197:573-579.