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FEATURE ARTICLES

Intermittent ICS Use Prevents Asthma Exacerbations in Preschoolers

New approaches are needed to better prevent severe asthma exacerbations in children under age 6. Most preschool children with recurrent wheezing have attacks of viral-triggered wheezing that are intermittent but potentially severe. The authors analyzed available data on three suggested strategies to prevent severe exacerbations in preschool-aged children with recurrent wheezing.

A literature search identified 22 randomized controlled trials evaluating interventions to prevent severe exacerbations in children aged 6 years or younger. The studies included a total of 4,550 children with asthma or recurrent wheezing. The interventions of interest were daily inhaled corticosteroids (ICS), intermittent ICS, and montelukast, with active or placebo comparison treatments. Meta-analyses were performed, focusing on the outcome of exacerbations requiring systemic steroids.

Fifteen studies provided data on 3,278 children assigned to daily ICS or placebo. Meta-analysis showed fewer exacerbations with daily medium-dose ICS: risk ratio 0.70, number needed to treat (NNT) 9. A subgroup analysis of data from eight studies included 2,505 children with persistent asthma assigned to daily ICS or placebo. Daily ICS reduced exacerbations, with an RR of 0.56 and NNT of 11. Analysis of 202 children from one trial found a similar effect of daily ICS compared to montelukast: RR 0.59.

Another subgroup analysis included 422 children with intermittent asthma or viral-triggered wheezing assigned to pre-emptive, high-dose intermittent ICS versus placebo. The results suggested that intermittent ICS reduced exacerbations: RR 0.65, NNT 6. • • •

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MERCK TEVA Respiratory

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

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Journal of 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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The systematic review supports the use of daily ICS to prevent severe exacerbations in preschool-aged children with persistent asthma. It also provides "strong evidence" for intermittent ICS to prevent exacerbations in children with intermittent asthma or viral-triggered wheezing. Further direct comparisons of treatment strategies for preschoolers with recurrent wheezing are needed.

COMMENT: Finally, an effective, evidence-based treatment to prevent exacerbations of viral-triggered wheezing in the challenging-to-treat population of preschoolers! A subgroup analysis of five studies involving 422 preschoolers with intermittent asthma or recurrent viral-triggered wheezing found strong evidence to support the efficacy of intermittent ICS use for 7 to 10 days to reduce risk of severe exacerbations (35% risk reduction, with an NNT of 6). This meta-analysis underscores the use of intermittent ICS as a yellow-zone intervention in persistent as well as intermittent asthma.

C.D.

Kaiser SV, Huynh T, Bacharier LB, et al: Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. Pediatrics. 2016;137:e20154496.

Keywords: asthma (child), exacerbations, prevention

Nasopharyngeal Microbiome Links RSV Infection with Asthma Risk

Early infection with respiratory syncytial virus (RSV) is known to be associated with the development of childhood asthma, although the underlying mechanism is unknown. This study assessed changes in the nasopharyngeal microbiome associated with RSV.

The study used nasal wash samples from 99 infants with confirmed acute respiratory infection with RSV and 99 healthy infants. Both groups were drawn from a prospective study that included respiratory illness surveillance during the infants' first winter; median age was 22 weeks for the infants with RSV and 5 weeks for healthy infants. The nasopharyngeal microbiome was compared between groups, based on bacterial 16S ribosomal RNA sequencing.

Most bacterial genera were significantly different between groups. *Staphylococcus* and *Corynebacterium* were more abundant in healthy infants, while *Haemophilus, Moraxella,* and *Streptococcus* were more abundant in those with RSV infection. Infection with RSV was associated with reduced richness at both the genus and operational taxonomic unit level. The results were similar on subgroup analysis of infants who were closer in age (median 9 to 10 weeks).

The results suggest shifts in the nasopharyngeal microbiome associated with initial RSV infection in infants. The predominant genera associated with RSV are similar to those previously associated with increased asthma risk. Further studies are needed to explore how RSV-related changes in microbiome might contribute to childhood asthma risk.

COMMENT: The changes in the airway microbiome associated with RSV infection may provide insight into the RSV-associated increased risk of asthma. Further work will help us better define and identify infants at risk for developing asthma at the time of first infection.

B.E.C.

Rosas-Salazar C, Shilts MH, Tovchigrechko A, et al: Nasopharyngeal microbiome in respiratory syncytial virus resembles profile associated with increased childhood asthma risk. Am J Respir Crit Care Med. 2016;193:1180-1183.

Keywords: asthma (child), microbiome, RSV

For Food Allergy Diagnosis, Ratio of Component-Specific to Total IgE Unhelpful

Component-resolved diagnosis can improve prediction of the outcomes of oral food challenge (OFC) to peanut and hazelnut. Information on total IgE, as an indicator of atopy, might improve the accuracy of component-specific IgE measurement. This study evaluated the ratio of component- or allergen-specific IgE to total IgE in predicting the results of OFC.

The multicenter study included 207 children with suspected peanut allergy and 142 with suspected hazelnut allergy. Each underwent measurement of specific IgE to peanut and hazelnut and to their component allergens, as well as total IgE. Ratios of specific to total IgE were evaluated for discriminative and predictive value in diagnosing food allergy.

Peanut OFC provoked symptoms in 43% of children and hazelnut challenge in 31%. Component-specific to total IgE ratios did not improve discrimination. Area under the curve was 0.93 with Ara h 2-specific IgE versus 0.92 for Ara h 2-specific/total IgE and 0.89 for Cor a 14-specific IgE versus 0.87 for Cor a 14-specific/total IgE ratio. At an Ara h 2-specific IgE level of 0.35 kU/L, the likelihood of positive peanut OFC was 16% for children with a total IgE level greater than 500 kU/L versus about 50% for those with low (less than 100 kU/L) or medium (100 to 500 kU/L) levels. At the same value for Cor a 14-specific IgE, the figures were 7% with high total IgE levels versus about 33% with low to medium total IgE levels. The predictive value of these approaches was independent of age, sex, eczema, and other patient characteristics.

In children with suspected peanut or hazelnut allergy, raw Ara h 2- and Cor a 14-specific IgE values are the best predictors of response to OFC. This suggests that food challenge may not be necessary in children with very high specific IgE levels. Information on the ratio of component-specific to total IgE does not improve predictive value, although children with high total IgE levels may have a lower probability of response at a given component-specific IgE level.

COMMENT: Oral food challenge is the gold standard for diagnosis of food allergy. Some have suggested that total IgE level can help predict results of OFC. These data from several European centers showed that raw allergen-specific component levels, using Ara h2 for peanut and Cor a 14 for hazelnut, were the best overall predictors for positive OFC in sensitized children. Interestingly, when the groups were stratified by total IgE level, those with IgE greater than 500 kU/L had a reduced probability of positive OFC, compared to those with medium or low total IgE levels. Predicting outcomes of OFC in children with food allergy is challenging.

S.M.F.

Grabenhenrich L, Lange L, Härtl M, et al: The component-specific to total IgE ratios do not improve peanut and hazelnut allergy diagnoses. J Allergy Clin Immunol. 2016;137:1751-1760.

Keywords: component testing, diagnosis, food allergy

Prenatal Omega-3 Fatty Acids: Not Fishy Enough

Randomized trial data suggest that prenatal supplementation with Ω-3 long-chain polyunsaturated fatty acids (LCPUFA) can reduce the incidence of allergy in young children at risk. This clinical trial with long-term follow-up evaluated the effects of prenatal Ω-3 LCPUFA supplementation on IgE-associated childhood allergic disease.

The "Docosoahexanoic Acid to Optimize Mother Infant Outcome" (DOMInO) trial enrolled pregnant women whose unborn child had a family history of allergic disease. One group of mothers was assigned to prenatal supplementation with Ω-3 LCPUFA fish oil capsules (containing docosahexanoic acid 800 mg/d and eicosapentaenoic acid 100 mg/d); the other group received vegetable oil capsules. Allergic disease symptoms and allergic sensitization were evaluated at age 6 in 706 children.

At age 6, there was no difference in the percentage of children with any type of IgE-associated allergic disease: 31.5% in both groups. The incidence of wheezing with sensitization at age 6 was 15% overall, and was also similar between groups. Skin-prick testing showed a reduction in house dust mite sensitization in the intervention group: 13.4% versus 20.3%, adjusted relative risk 0.67. Sensitization to other allergens was similar between groups.

The DOMInO trial shows no reduction in allergic disease among early school-age children assigned to prenatal Ω-3 LCPUFA supplementation. There is evidence of a reduced rate of house dust mite sensitization in the supplementation group. Further studies evaluating other strategies involving Ω-3 LCPUFA supplementation are warranted.

COMMENT: Evidence from randomized controlled trials in early infancy suggests that prenatal supplementation with Ω-3 LCPUFAs reduces the incidence of allergic disease in early childhood (1 to 3 years). But is this protective effect sustained? Alas, follow-up of children with a family history of allergic disease enrolled in an Australian prospective cohort study failed to show a protective effect of prenatal fish oil supplementation at age 6 years. Perhaps strategies such as supplementing through conception (or preconception) and continuing through breastfeeding may need to be evaluated.

C.D.

Best KP, Sullivan T, Palmer D, et al: Prenatal fish oil supplementation

and allergy: 6-year follow-up of a randomized controlled trial. Pediatrics. 2016;137:e20154443.

Keywords: fish oil, prevention

LABA-LAMA Is Effective in Preventing COPD Exacerbations

For patients with chronic obstructive pulmonary disease (COPD), the combination of an inhaled corticosteroid (ICS) plus a long-active beta-agonist (LABA) or long-acting muscarinic antagonist (LAMA) is recommended to prevent exacerbations. Dual bronchodilator treatment with a LABA and a LAMA has been recommended as an alternative long-term ICS use. This randomized trial evaluated the use of a LABA-LAMA combination for COPD patients at risk of exacerbations.

The multicenter "EFfect of Indacaterol Glycopyrronium Vs Fluticasone Salmeterol on COPD Exacerbations" (FLAME) trial included 3,362 COPD patients with one or more exacerbations in the previous year. One group received a LABA-LAMA combination, indacaterol 110 μg plus glycopyrronium 50 μg once daily; controls received a LABA-ICS combination, salmeterol 50 μg plus fluticasone 500 μg twice daily. Annual overall COPD exacerbation rate was the main outcome of interest.

The rate of all COPD exacerbations was lower with the LAMA-LABA combination compared to ICS-LABA: 3.59 versus 4.03 per year, rate ratio 0.89. In addition, LAMA-LABA was associated with a longer time to first exacerbation: 71 versus 51 days, hazard ratio 0.84. The LAMA-LABA combination was also associated with a reduced risk of moderate to severe COPD exacerbations: 0.98 versus 1.19 per year, rate ratio, 0.83; and a longer time to first moderate to severe exacerbation, HR 0.78.

The advantage of the LABA-LAMA combination was unaffected by the baseline blood eosinophil count. Safety analysis showed no significant difference in adverse events or mortality between groups. Pneumonia was more common in the ICS-LABA group: 4.8%, compared to 3.2% with LABA-LAMA.

A combination of the LABA indacaterol with the LAMA glycopyrronium reduces the exacerbation rate in COPD patients at risk, compared to the ICS fluticasone plus the LABA salmeterol. Adverse events are similar between the two treatments. The authors discuss the clinical implications for COPD management, particularly in patients with a history of exacerbations.

COMMENT: The role of an ICS plus LABA or LAMA as first-line therapy for COPD patients at risk of exacerbations has been delineated in the GOLD guidelines. The FLAME trial showcases the potential new role of a LABA-LAMA (fixed dose) in the prevention of COPD exacerbations. The indacaterol-glycopyrronium regimen was found more effective than salmeterol-fluticasone in reducing the rate of exacerbations. Interestingly, contrary to other studies, the researchers were unable to demonstrate utility of using an eosinophil count of greater than 2% as a biomarker to favor use of an ICS-containing regimen. In an accompanying editorial (N Engl J Med. 2016;374;2284-2286), Donohue speculates whether lung function improvement and reduction in exacerbation rates is enough to justify switching patients from LABA-ICS to a LABA-LAMA regimen. Criteria to identify those for whom an ICS-containing regimen may be preferred remain to be determined.

C.D.

Wedzicha JA, Banerji D, Chapman KR, et al: Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med. 2016;374:2222-2234.

Keywords: COPD, LABA, LAMA

Sputum IL-13: A Better Biomarker for Asthma?

Interleukin-13 (IL-13) is a Th2-type cytokine that may be a useful therapeutic target in uncontrolled asthma. Sputum IL-13 was investigated as a biomarker for asthma control, compared to sputum eosinophil count and exhaled nitric oxide.

The study included 170 patients seen at two Greek asthma clinics. All were assessed using the Asthma Control Test (ACT) and lung function testing. Sputum IL-13 and eosinophils and exhaled NO were evaluated as indicators of ACT score.

Based on an ACT score of less than 20, asthma was not well-controlled in 31 of 170 patients. Median sputum IL-13 was 78 pg/mL in patients with well-controlled asthma, compared to 213 pg/mL in those with not-well-controlled asthma. Median values were 76 pg/mL in 123 patients with mild to moderate asthma versus 156 pg/mL in 47 patients with severe refractory asthma. Sputum eosinophils and exhaled NO were both higher in patients whose asthma was not well-controlled.

On receiver operating characteristic analysis, IL-13 had the highest diagnostic performance. Area under the curve was 0.92 for sputum IL-13, compared to 0.65 for both sputum eosinophils and exhaled NO.

Sputum IL-13 is superior to sputum eosinophil count or exhaled NO in identifying patients with versus without well-controlled asthma, based on the ACT. Sputum IL-13 may be a useful biomarker not only in mild to moderate asthma but also severe refractory asthma.

COMMENT: Finding the best biomarker for asthma is akin to searching for the Holy Grail. This study from Athens studied 123 patients with mild to moderate asthma and 47 with severe asthma and correlated asthma control with sputum eosinophils, exhaled NO, and sputum IL-13. Sputum IL-13 performed very well; it had a positive predictive value of 95% for well-controlled asthma and was superior to the other biomarkers. It also did a better job discerning mild-moderate from severe asthma subjects. While the data are promising, any biomarker requiring induced sputum is cumber- • • •

some. Further refinements and larger studies will be required to determine if indeed the Holy Grail has been discovered.

D.A.K.

Tsilogianni Z, Hillas G, Bakakos P, et al: Sputum interleukin-13 as a biomarker for the evaluation of asthma control. Clin Exp Allergy. 2016;46:923-931.

Keywords: asthma (adult), biomarkers, IL-13

Should We Explore Inhaled Biologics for Asthma?

Anti-interleukin-5 (IL-5) therapy with mepolizumab reduces blood and sputum eosinophilia, while reducing steroid requirements, in patients with severe asthma. It's unclear whether the development of airway eosinophilia in these patients is related to local maturational processes or to recruitment of mature cells from the circulation. This study evaluated the role of local eosinophilopoietic processes in patients with prednisone-dependent severe asthma.

The researchers analyzed the number and growth potential of eosinophil-lineage-committed progenitors (EoPs) in 21 patients with severe eosinophilic asthma. Nineteen patients with mild asthma, 8 with COPD, and 8 healthy controls were studied for comparison. The severe eosinophilic asthma patients were drawn from a randomized, placebo-controlled trial of mepolizumab therapy (six monthly 100 mg sc injections).

Compared to all other groups, the severe asthma patients had higher numbers of mature eosinophils and EoPs in sputum. Compared to patients with mild asthma, the proportional frequency of sputum EoPs was elevated tenfold in the severe-asthma group. In culture, EoPs from blood of severe asthma patients had a greater response to IL-5 than EoPs from patients with mild asthma. Mepolizumab therapy was associated with a reduction in blood eosinophils with increased numbers of EoPs, suggesting that systemic eosinophilopoiesis was blocked by the anti-IL-5 agent. Mature eosinophils and sputum EoP numbers were unaffected by mepolizumab, as was the required prednisone maintenance dose.

The findings suggest an exaggerated eosinophilopoietic process in the airways of patients with severe, prednisone-dependent asthma. While mepolizumab therapy reduces the attenuated systemic differentiation of eosinophils, it does not prevent local eosinophil maturation. Studies targeting local IL-5-driven eosinophil differentiation within the lung are needed.

COMMENT: As we advance in our use of biologic agents such as mepolizumab, we must continue to explore the optimal delivery of the agent. In this study, although treatment with mepolizumab resulted in significant attenuation of systemic differentiation of eosinophils, it did not suppress local airway eosinophil differentiation into mature cells. The authors suggest that targeting eosinophil differentiation locally in the lung may be necessary for "optimal control" of airway eosinophils in asthma.

J.J.O.

Sehmi R, Smith SG, Kjarsgaard M, et al: Role of local eosinophilopoietic processes in the development of airway eosinophilia in prednisone-dependent severe asthma. Clin Exp Allergy. 2016;46:793-802.

Keywords: asthma (adult), asthma (severe), biologics

Can We Make a Hypoallergenic Peanut?

Efforts at peanut oral immunotherapy have been hindered by high rates of treatment-related adverse events and withdrawal. Previous reports have suggested that boiling may lower the allergenicity of peanuts, potentially lowering the risk of reactions. This study evaluated the effects of prolonged boiling on peanut allergenicity and T-cell reactivity.

The investigators boiled raw peanuts for 0.5, 1, 2, 4, and 12 hours. Peanut protein was extracted, and changes to peanut allergens and IgE reactivity were compared to commercial raw peanut extract. T-cell responses were assessed by proliferation of CD4+/CF25+/CD134+ T-cells from subjects with and without peanut allergy.

Peanut allergenicity decreased progressively with longer boiling times. On inhibition enzyme-linked immunosorbent assay, IgE-binding capacity was decreased by eight times after 2 hours of boiling and by 19 times after 12 hours of boiling. Decreased allergenicity was associated with allergen leaching into the boiling water, allergen fragmentation, and denaturation of conformational epitopes.

Longer boiling times were also associated with an increased number of allergen peptides—up to 42 times more unique peptides after 12 hours of boiling. T-cell activation and proliferation assays showed no difference in response to raw peanuts versus peanuts boiled for 2 or 12 hours. On skin-prick tests in 20 peanut-allergic children, wheal size was reduced by 55% using extract from peanuts boiled 2 hours and 36% for peanuts boiled for 4 hours.

Prolonged boiling leads to progressive reduction of peanut allergenicity, but no change in T-cell reactivity. Thus hypoallergenic boiled peanuts may be a promising alternative for oral immunotherapy. Boiling for 2 to 12 hours may be needed to achieve these effects, in contrast to previous studies using boiling periods of no more than 1 hour.

COMMENT: This article indicates the potential for a hypoallergenic form of peanut through prolonged boiling. Although boiling resulted in reduced peanut allergenicity, it did not affect T-cell reactivity. How boiling reduces allergenicity is uncertain, but it could be due to leaching of peanut allergens into the cooking water, fragmentation of proteins through hydrolysis, and denaturing of the three-dimensional structure. Could this be like baked egg for the treat-

ment of egg allergy? Certainly, more is to come.

J.J.O.

Tao B, Bernardo K, Eldi P, et al: Extended boiling of peanut progressively reduces IgE allergenicity while retaining T cell reactivity.
Clin Exp Allergy. 2016;46:1004-1014.

Keywords: boiled peanut, peanut allergy, oral immunotherapy

Can Wine Cause Reactions in Patients with Shrimp Allergy?

Chitosan, a product derived from the chitin in arthropod exoskeletons, is sometimes used in wine processing. This has raised concerns about the possibility of reactions to wine in patients with seafood allergy.

The authors assessed reactions to chitosan-processed wine in 13 patients with IgE-mediated sensitization and a history of anaphylactic reactions to shrimp. One patient had a positive skin-prick test (SPT) result to chitosan-processed wine, as well as to a control wine preserved with sulfur dioxide. However, in double-blind challenges, none of the shrimp-allergic patients (or 6 nonallergic controls) had an immediate or late-phase response to either of the study wines.

The results suggest that patients with shrimp and seafood allergy may safely drink chitosan-processed wines, with a low risk of triggering a reaction. Although small, the study adds to the scarce data on patients with shrimp allergy.

COMMENT: Chitosan is produced when chitin, part of the exoskeleton of crustaceans, is deacetylated. Some patients may avoid wine produced with chitosan due to fear of an allergic reaction. This small study looked at whether patients with shrimp anaphylaxis could tolerate chitosan-processed wine. The authors remind us that use of SPT alone is not sufficient in this situation—one patient who tested positive on SPT was able to tolerate oral challenge. Chitosan-processed wine appears to be safe for patients with shrimp anaphylaxis.

V.H.-T.

Amaral L, Silva D, Couto M, et al: Safety of chitosan processed wine in shrimp allergic patients. Ann Allergy Asthma Immunol. 2016;116:461-477.

Keywords: seafood allergy

Urine Test May Be Noninvasive Marker for EoE

The current standard for diagnosis and monitoring of eosinophilic esophagitis (EoE) is esophageal biopsy with eosinophil count. Developing a noninvasive, cost-effective biomarker of eosinophil activation would be an important contribution to clinical management. This study assessed urinary 3-bromotyrosine (3-BT) measurement as a possible biomarker of EoE.

The investigators developed an assay called the Eosinophil Quantitated Urine Kinetic (EoQUIK), a mass spectrometry-based technique for measurement 3-BT in creatinine-normalized urine samples. A proof-of-concept study included 27 patients meeting clinical and biopsy criteria for EoE, along with 24 atopic and 24 nonatopic controls.

On the EoQUIK, normalized 3-BT measurements varied significantly between groups. In the EoE patients, median urinary 3-BT level was 93 times higher than in the nonatopic control group, and 13 times higher than in atopic controls. At selected cutoff values, EoQUIK identified EoE patients with specificity and negative predictive value of 100% versus nonatopic controls, and with specificity of 79% and negative predictive value of 90% versus atopic controls.

Subjects with a urine 3-BT level greater than 20 pg/400 mg of creatinine were 4.8 times more likely to have EoE compared to atopic controls, in a logistic regression model controlled for race and sex. In the atopic control group, being tested during an atopic disease flare was not associated with any difference in urinary 3-BT.

Measuring urinary 3-BT using the EoQUIK might provide a simple, noninvasive biomarker for evaluation of patients with possible EoE. Although sensitivity is "modest," a high 3-BT raises the index of suspicion for EoE. Larger clinical studies are needed to validate the EoQUIK test.

COMMENT: Patients with EoE are in need of some noninvasive measure of disease. Prior studies have shown the utility of urinary 3-BT as a marker of eosinophil activation in predicting asthma. Urinary 3-BT is an exciting assay that may aid the practicing allergist as a promising marker for diagnosis of EoE. It gives patients and providers alike hope in a disease where invasive tests are currently needed for diagnosis and follow up. Future studies will investigate whether 3-BT can be used for long-term monitoring of disease activity and response to treatment in patients with EoE.

V.H.-T.

Cunnion KM, Willis LK, Minto HB, et al: Eosinophil quantitated urine kinetic: a novel assay for assessment of eosinophilic esophagitis.
Ann Allergy Asthma Immunol. 2016;116:435-439.

Keywords: biomarkers, EoE

Gun Violence: An Ethno-Specific Risk Factor in Asthma

Both in Puerto Rico and on the US mainland, Puerto Rican children are at increased risk of asthma. Previous studies have linked exposure to gun violence and African ancestry to an increased risk of childhood asthma in this racial/ethnic group. This study assessed the possible interaction between these two asthma risk factors in Puerto Rican children.

The case-control study included two groups of school-aged (9 to 14 years) Puerto Rican children: 472 living in Puerto Rico and 275 in Connecticut. Children who ...

reported hearing gunshots more than once were considered exposed to gun violence. Percentage of African ancestry was estimated from DNA genotyping studies. Interactions between these two risk factors and parent reports of physician-diagnosed asthma and wheezing and serum IgE levels were analyzed.

On multivariate analysis, the effect of African ancestry on childhood asthma risk was modified by exposure to gun violence. For each one-quartile increase in percentage of African ancestry, there was a 45% increase in the odds of asthma among children exposure to gun violence. In contrast, percentage of African ancestry was unrelated to asthma risk among children not exposed to gun violence. A similar interaction was noted for higher total IgE. Overall, exposure to gun violence was reported by about 59% of cases with asthma and 47% of controls.

In Puerto Rican children, exposure to gun violence is a potentially preventable modifier of the relationship between African ancestry asthma, and atopy. While the mechanisms of these associations are unclear, Puerto Rican children with higher African ancestry may be more susceptible to harmful health effects of gun violence.

COMMENT: Gun violence is an unfortunate topic of headlines lately. It has also been shown to be a risk factor for childhood asthma. This study involving a large number of children from Puerto Rico found that the amount of African ancestry had an increasing affect on the risk for asthma and elevated IgE—but only in children who were also exposed to gun violence. The reason for this association is not well understood. However, it speaks to the complexity of gene-environment interactions, as well as the fact that some ethnicities cannot be considered homogeneous.

D.A.K.

Rosas-Salazar C, Han Y-Y, Brehn JM, et al: Gun violence, African ancestry, and asthma: a case-control study in Puerto Rican children.
Chest. 2016;149:1436-1444.

Keywords: asthma (child), risk factors

Phase IIb Peptide Immunotherapy Shows Promise

An approach using contiguous overlapping peptides (COPs) derived from Bet v 1 has been developed with the aim of providing effective birch pollen immunotherapy with improved safety and a shorter duration of treatment. A previous phase I/IIa trial showed good clinical tolerability with the 3-COP product. The authors report a phase IIb, placebo-controlled, dose-finding trial of immunotherapy using Bet v 1 COPs.

The study included 239 adults with birch pollen allergy and rhinoconjunctivitis. Five weeks before birch pollen season, they received Bet v 1 COPs in one of two dose regimens (50 or 100 μg) or placebo in five subcutaneous injections. Adverse events, rhinoconjunctivitis symptom and medication scores, and quality of life were compared between groups.

Symptom and medication scores improved in both Bet v 1 COP groups, although the improvement was significant (26 percent) only in the 50 μg dose group. Nighttime nasal symptom scores also improved in both active immunotherapy groups, as did quality of life. Specific IgG_4 and IgE responses were similar between the two Bet v a COP groups. Systemic adverse events were more common in the 100 μg group.

The results support the safety and efficacy of preseasonal birch pollen immunotherapy using the 3-COP product. Clinical responses appear better with the lower of the two doses tested, with a small risk of systemic reactions and significant immunogenic effects. This approach may provide effective birch pollen immunotherapy in a substantially shorter treatment time.

COMMENT: Allergen immunotherapy is the only truly disease-modifying therapy available for our patients. Recent efforts have focused on improving its efficacy, safety and efficiency. This study used a formulation of contiguous overlapping peptides from Bet v 1 in patients with birch allergic rhinoconjunctivitis. After a test dose, the 3-COP product was administered in just four subcutaneous doses over a 2-month period. The results show an impressive clinical response to one of the doses—surprisingly, the lower dose. The safety profile seems reasonable and the IgG_4 responses impressive. Newer approaches for immunotherapy for allergic diseases are on the horizon. We need to be aware of these and understand how they will help our patients and potentially impact our practices.

S.M.F.

Spertini F, DellaCorte G, Kettner A, et al: Efficacy of 2 months of allergen-specific immunotherapy with Bet v 1-derived contiguous overlapping peptides in patients with allergic rhinoconjunctivitis: results of a phase IIb study.
J Allergy Clin Immunol. 2016;138:162-168.

Keywords: birch pollen allergy, subcutaneous immunotherapy

Is Exhaled NO a Marker of Air Pollution Effect?

Exposure to traffic-related air pollution (TRAP) has known adverse respiratory effects, but the mechanisms of those effects remain unclear. While previous studies have looked at associations between pollutant exposure and exhaled nitric oxide, inflammatory responses to TRAP may differ in the distal versus proximal airways. This study analyzed the relationship between short-term TRAP exposure and localized inflammation of the lower respiratory tract in children.

The study included 1,365 children, aged 12 to 15, from the Southern California Children's Health Study. Children underwent measurement of exhaled NO at four flow rates while breathing schoolroom air. Indoor NO was measured hourly as a marker of TRAP exposure in the indoor • • •

microenvironment. Associations between indoor NO and airway and alveolar sources of exhaled NO were analyzed.

Higher acute exposure to indoor TRAP was associated with higher measurements of alveolar NO. For each 10 ppb increase in indoor NO concentration at the time of testing, average alveolar NO concentration increased by 0.10 ppb—7.1% higher than the mean. The same increment was associated with a 4.0% increase in maximum airway wall NO flux and a 0.2% reduction in airway wall tissue diffusing capacity.

The findings suggest a significant airway response to indoor NO exposure, most pronounced in the distal airways. The results are consistent with an acute distal airway inflammatory response to TRAP. The associations might reflect higher deposition of ultrafine particles in the distal versus proximal airways.

COMMENT: Indoor NO depends on outdoor NO. In this study, TRAP exposure was linked to distal airway inflammation, as measured by elevated alveolar NO. The accompanying editorial (Eur Respir J. 2016;47:1348-1356) provides insight by calling into question some of the conclusions reached. This is a major contribution to our understanding of the site of airway inflammation in children exposed to traffic-related air pollution. The study is an extension of previous observations from a cohort of children studied in Southern California over the last two decades.

B.E.C.

Eckel SP, Zhang Z, Habre R, et al: Traffic-related air pollution and alveolar nitric oxide in southern California children. Eur Respir J. 2016;47:1348-1356.

Keywords: air pollution, biomarkers, exhaled NO

Differing Neurophenotypes of Cough in Airway Disease

Coughing is a symptom of most airway diseases, including chronic obstructive pulmonary disease (COPD). While activation of vagal afferents is one possible mechanism, alterations of the neuronal pathways controlling cough may be involved in some conditions. The authors performed a clinical study and a series of preclinical studies to elucidate cough responses to irritants in patients with COPD versus other groups.

In the clinical study, cough responses to inhaled capsaicin, citric acid, prostaglandin E_2, and bradykinin were evaluated in 18 COPD patients, 22 asthma patients, 22 patients with refractory cough, 20 healthy smokers, and 21 healthy volunteers. The researchers then assessed the vagus/airway nerve and cough responses in models involving guinea pigs exposed to cigarette smoke.

Compared to healthy controls, COPD patients had increased cough responses to capsaicin but reduced responses to PGE_2. The various patient groups showed differing patterns of modulation of cough responses; responses to capsaicin, citric acid, and PGE_2 were all independent predictors of diagnostic group.

The patterns in humans were consistent with models showing that capsaicin induced a higher number of coughs in animals exposed to cigarette smoke. That finding was supported by ex vivo studies showing similar increased responses in vagus nerve and neuron cell bodies in the vagal ganglia. Cigarette smoke was associated with lower responsiveness to PGE_2.

The findings suggest that cigarette smoke can induce "phenotypic switches" in the function of airway nerves, consistent with the cough responses associated with COPD. The concept of "disease-specific neurophenotypes" may help in identifying new therapeutic targets in airway disease.

COMMENT: Cough is reported by 12% of the adult population and is the most common reason for office visits to respiratory practitioners. The neurophenotypes of chronic cough are evolving, which will lead to precision treatments for cough. This article and accompanying editorial (Am J Respir Crit Care Med. 2016;193:1324-1326) provide insight into the complexity of the pathophysiology of chronic cough. Answers are not currently present, but it seems clear that hope is on the horizon.

B.E.C.

Belvisi MG, Birrell MA, Khalid S, et al: Neurophenotypes in airway diseases: insights from translational cough studies.
Am J Respir Crit Care Med 2016;193: 1364-1372.

Keywords: COPD, cough, phenotypes, smoking

Skin Testing for Molds: Duplicate Tests Needed?

Mold allergy can be difficult to diagnose because of the lack of standardized test material and the sharply reduced number of commercially available skin test solutions. A recent study raised questions about differences in skin-prick tests (SPTs) from different manufacturers, and their comparability with the results of specific IgE testing. These issues were addressed in a European multicenter study.

The study included 169 patients with mold exposure and/or mold-induced respiratory symptoms, drawn from 12 German and one Polish clinic. Skin-prick tests from four manufacturers underwent biochemical analysis and were used for duplicate testing on patients' arms. Specific IgE testing for corresponding mold species and for mold mix was performed as well. Based on their findings, the investigators sought to develop a feasible testing strategy for diagnoses of mold allergy.

Positive results for mold sensitization were found in 54% of patients by SPT versus 33% by specific IgE measurement. For all but five SPT solutions, concordance of double positive SPT results was less than 80%; for six solutions, concordance was less than 60%. Concordance between double SPTs and with specific IgE was significantly associated with the antigen content of SPT products. Compared to specific IgE, all • • •

SPTs had test efficiencies greater than 80%. However, except for *Alternaria alternata,* test sensitivity and positive predictive value varied by up to 20%.

Despite their limitations, current SPTs are sensitive tools for evaluation of suspected mold allergy. The authors discuss some recommended testing strategies, including SPT for *A. alternata, Aspergillus fumigatus,* and *Penicillium chrysogenum* (the three most commonly detected molds) plus specific IgE measurement for mold mix.

COMMENT: It is well-recognized that products for mold skin testing are highly variable. This study from Europe evaluated the results of skin tests from four different manufacturers in 168 patients. It also included duplicate skin tests performed on the forearm. Skin testing was much more sensitive than mold-specific IgE, detecting positives 1.6 times more often. There was large variability in skin test reactivity between manufacturers. Concordance between individual mold skin tests was poor overall; the authors suggest that duplicate testing for the three most common molds along with an in vitro mold mix is an efficient way of testing. A study using US mold extracts with tests performed on the back—a more sensitive area for skin tests—would be interesting to confirm the generalizability of these findings.

D.A.K.

Kespohl S, Maryska S, Bunger J, et al: How to diagnose mould allergy? Comparison of skin prick tests with specific IgE results.
Clin Exp Allergy. 2016;46:981-991.

Keywords: diagnosis, mold allergy, skin-prick testing

High Ω-3 PUFAs Help Explain Protective Effect of Farm Milk

Consumption of unprocessed cow's milk may contribute to the lower rates of asthma and allergies for children living on farms. The components of cow's milk that might be responsible for this effect are unknown. This issue was addressed as part of a long-term follow-up study of children growing up on farms.

The analysis included 934 children from the European "Protection Against Allergy–Study in Rural Environments" (PASTURE) study, which included follow-up from birth to age 6. In this cohort, milk consumption was assessed by annual questionnaire. At age 4, samples of the children's "usual" milk were collected for analysis, along with serum samples. Physician-diagnosed asthma was assessed at age 6. In a nested case-control study, 42 different fatty acids were compared in milk samples for 35 asthmatic and 49 nonasthmatic children.

Children who consumed unprocessed farm milk at age 4 were less likely to have asthma at age 6: adjusted odds ratio 0.26, compared to children who drank milk from stores. The protective effect was partly related to the increased fat content of farm milk, especially Ω-3 polyunsaturated fatty acids (Ω-3 PUFAs): adjusted odds ratio 0.29. This inverse association was not explained by any potential confounder.

The longitudinal analysis confirms that consuming unprocessed milk from farms during childhood is associated with a lower risk of asthma at school age. This protective effect may at least partly reflect the higher levels of Ω-3 PUFAs in farm milk, which may amount to an "anti-inflammatory treatment of subclinical asthma." Interventional studies will determine whether milk fortified with Ω-3 PUFAs might be helpful for primary or secondary prevention of childhood asthma.

COMMENT: Although current guidelines recommend against the use of raw, unpasteurized cow's milk in early childhood, it is well-known that raw milk has a protective effect reducing the risk for developing asthma and allergies. Using data from a case-controlled group from the PASTURE cohort, these European researchers found that the children consuming raw milk with higher ω-3 PUFA content were less likely to develop asthma compared to those consuming milk with lower Ω-3 PUFAs. The authors propose that the anti-inflammatory properties of Ω-3 PUFAs could explain some of the protective benefit for allergies. Will this lead to Ω-3 PUFA fortification of processed milk? We'll see….

S.M.F.

Brick T, Schober Y, Böcking C, et al: ω-3 fatty acids contribute to the asthma-protective effect of unprocessed cow's milk.
J Allergy Clin Immunol. 2016;137:1699-1706.

Keywords: asthma (childhood), farms, hygiene hypothesis, prevention

Ethical Issues in SCID Treatment

Hematopoietic stem cell transplantation (HSCT) is a potentially effective treatment for severe combined immunodeficiency (SCID). However, treatment carries significant risks with short- and long-term morbidity. An expert panel discusses a case in which parents refused consent to HSCT in a child with SCID.

A 3-month-old boy with hypoxic respiratory failure was diagnosed with SCID caused by a homozygous *RAG1* mutation. Unrelated matched donor HSCT was proposed; parents were told that without this definitive treatment, the child would probably die within a year. After discussion, the parents declined HSCT. Believing that the financial and medical burdens outweighed the chances of success, they preferred to take their child home and provide comfort care until death. The treating physicians sought an ethics consultation, including the possibility of seeking protective custody.

The experts weigh the complex issues raised by this case, starting with the need to understand in detail the parents' reasons for refusing treatment. The conditions justifying state interference with parental decision making are outlined; the child's case clearly meets some but not all of them. Ethics referral can alleviate clinical anxiety and transfer responsibility from the treating clinicians, but poses a challenge to • • •

a trusting relationship with parents. The potential for immediate or future litigation needs to be considered, along with the emotional and psychological risks of legally coerced HSCT.

The experts emphasize that there is no "right answer" in such a complex case: "All the choices are bad, all the options are legal." A concluding statement suggests that judicial review is necessary in this case—acknowledging that the deeply personal issues involved also have societal implications.

COMMENT: In this well-articulated discussion, a team of experts in immunodeficiency, transplant care, and ethics discusses the nuances of responding to the ethical questions raised when parents choose not to have their child with SCID undergo lifesaving transplantation. With the increasing ability to detect SCID patients through statewide newborn screening, this is the type of ethical conundrum that allergists/immunologists may face.

C.D.

Nickels AS, Myers GD, Johnson L-M, et al: Can parents refuse a potentially lifesaving transplant for severe combined immunodeficiency? Pediatrics.2016;138:e20160892.

Keywords: ethics, HSCT, SCID

What Factors Affect Long-Term Prognosis in ACOS?

More information is needed on the long-term prognosis for patients with characteristics of both chronic obstructive pulmonary disease and asthma, or asthma-COPD overlap syndrome (ACOS). Data from a longitudinal population study were analyzed to assess the long-term outcomes of ACOS and other forms of chronic airway disease.

The study included 8,382 participants from the Copenhagen City Heart Study: 2,199 who had never smoked, 5,435 with a history of smoking, 158 with asthma, 320 with COPD, 68 with ACOS and early-onset asthma (before age 40), and 202 with ACOS and late-onset asthma (after age 40). The study definition of ACOS was self-reported asthma and a postbronchodilatatory FEV_1 to forced vital capacity ratio of less than 0.7, regardless of smoking history. The course of FEV_1 decline was studied over 18 years and the risk of hospitalization due to exacerbations or pneumonias and respiratory and all-cause mortality for 22 years.

In multivariable-adjusted models, FEV_1 declined by 27.3 mL/y in patients with ACOS and early-onset asthma—not significantly different from the 20.9 mL/y rate in healthy subjects with no history of smoking. In contrast, the 49.6 mL/y rate of decline in subjects with ACOS and late-onset asthma was greater than in either of these groups, and faster than the 39.5 mL/y rate in participants with COPD.

Subjects with ACOS and late-onset asthma were also at highest risk of hospital admissions due to exacerbations of asthma or COPD: hazard ratio 83.47, compared to 39.48 for ACOS with early-onset asthma, 23.80 for COPD, and 14.74 for asthma (compared to healthy subjects with no smoking history). Reductions in life expectancy were 12.8 years, 9.3 years,10.1 years, and 3.3 years, respectively.

The data highlight the poor long-term outcomes of ACOS, especially for patients with asthma onset after age 40. This group has an "extraordinarily poor" prognosis, with accelerated FEV_1 decline, high rates of exacerbations and pneumonia, and shorter survival. Evidence-based treatment options for patients with characteristics of both asthma and COPD are urgently needed.

COMMENT: We have much to learn about ACOS. This study demonstrates that the prognosis for patients with ACOS is overall quite poor. Further, when stratified by age of onset, those who develop symptoms after age 40 are likely to have greater morbidity, including loss of lung function, hospitalization for respiratory disease, and even shorter life expectancy than those who develop symptoms earlier in life. Unfortunately, numbers of patients in the ACOS group in this study were fairly small. More robust studies are sure to follow.

J.J.O.

Lange P, Çolak, Ingebrigtsen TS, et al: Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. Lancet Respir Med. 2016;4:454-462.

Keywords: ACOS, COPD, prognosis

Is Herbal Medicine Effective for Asthma?

Up to 80% of adults with asthma use some form of complementary medicine. While previous reviews have reported promising effects of herbal medicines for asthma, they have been limited by methodologic shortcomings of the studies included. The authors present an updated analysis of evidence on herbal medicines for adult asthma, including Chinese herbal medicines.

A comprehensive review of the literature identified 29 randomized trials of herbal medicines for adult asthma. The data suggested that, combined with medications, herbal medicines can improve lung function and asthma control while reducing exacerbations and bronchodilator use. In three placebo-controlled trials, herbal medicines improved lung function compared to pharmacotherapy. The benefits of the herbal medications evaluated—such as licorice root *(gan cao)* and astargali *(huang qi)*—may be related to anti-inflammatory effects, which have been demonstrated in animal models. The identified studies were of low overall quality, with a high risk of bias.

Within the limitations of available data, evidence suggests that herbal medicines can have positive effects in combination with pharmacotherapies for adult asthma. Especially with the high use of these products by patients with • • •

asthma, further studies on the effects of herbal medicine studies are needed.

COMMENT: Herbal medicine is poorly defined and has not been systematically evaluated in randomized trials for asthma. This systematic review concludes that adding an herbal supplement to conventional pharmacotherapies for adults with asthma leads to better outcomes. Unfortunately, herbal supplements are vaguely and heterogeneously defined. Randomized controlled trials of well-defined herbal medicines are needed to effectively evaluate their safety and efficacy in asthmatic adults.

C.C.R.

Shergis JL, Wu L, Zhang AL, et al: Herbal medicine for adults with asthma: a systematic review. J Asthma. 2016;53:650-659.

Keywords: asthma (adult), complementary and alternative medicine

Personalized Care and the Use of Mepolizumab

Two large trials, DREAM and MENSA, have found that anti-interleukin-5 (IL-5) therapy with mepolizumab lowers the risk of exacerbations in patients with severe eosinophilic asthma. Blood eosinophil count may predict the response to mepolizumab. This post hoc analysis of data from DREAM and MENSA compared responses to mepolizumab among patients with differing blood eosinophil thresholds.

The studies enrolled patients (age 12 years or older) with clinically diagnosed asthma, at least two exacerbations requiring systemic corticosteroids in the previous year, and evidence of eosinophilic airway inflammation. The post hoc analysis included 1,192 patients: 846 assigned to mepolizumab and 346 to placebo. The overall rate of mean exacerbations was 1.91 with placebo versus 1.01 with mepolizumab: rate ratio 0.53.

Exacerbation rates were analyzed in groups of patients stratified by baseline blood eosinophil count. The rate ratio for reduction in exacerbations increased from 0.48 for patients with a blood eosinophil count of 150 cells/μL or higher to 0.30 for those with a count of 500 cells/μL or higher. The predicted efficacy of mepolizumab was lower for patients with a baseline eosinophil count of less than 150 cells/μL. Improvement in lung function outcomes was greater for above the 500 cells/μL threshold; quality of life and asthma control benefits were also affected by baseline blood eosinophil counts.

For patients with severe eosinophilic asthma, the benefits of mepolizumab vary according to baseline blood eosinophil count. Clinically significant reductions in exacerbation rate appear at a count of 150 cells/μL, and increase at higher cell counts. Blood eosinophil count may be an important predictor of which patients are likely to benefit from mepolizumab.

COMMENT: With the addition of biologic agents to our asthma therapeutic armamentarium, it has never been more important to practice "personalized medicine." As we begin this quest for phenotypic discriminators, blood eosinophil count is an easily accessible and sensitive biomarker of asthma, with results available rapidly after collection. Ortega and colleagues show that a threshold of at least 150 cells/μL identifies patients with uncontrolled asthma (despite use of multiple controller therapies) who are likely to achieve reductions in exacerbation rate when mepolizumab was added to their regimen. Even further reductions in exacerbations are seen in patients with higher baseline blood eosinophil counts. Improvements in quality of life are reported as well.

J.J.O.

Ortega HG, Yancey SW, Mayer B, et al: Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. 2016;4:549-556.

Keywords: asthma (adult), biologics, biomarkers, exacerbations

Is Acupuncture a Useful Treatment for PAR?

Clinical studies have reported that acupuncture can reduce symptoms and improve quality of life in patients with persistent allergic rhinitis (PAR). However, little is known about the physiologic basis of these benefits. This trial evaluated acupuncture's effects on mucosal immune responses in patients with PAR.

The Australian randomized trial included 151 patients with moderate to severe PAR and confirmed sensitization to local grass pollens and/or house dust mite. Patients were assigned to weekly real or sham acupuncture, or no acupuncture. Various immune markers were measured over 4 weeks, along with clinical outcomes.

Real acupuncture was associated with a significant reduction in house dust mite-specific IgE: from 18.87 to 17.82 kU/L. No such reduction was seen in the sham or no acupuncture groups. There was also significant downregulation in proinflammatory neuropeptide substance P, within 18 to 24 hours after the first acupuncture session: from 408.74 to 90.77 pg/mL. Other markers were unchanged.

Real acupuncture was also associated with improvements in nasal obstruction and itch, sneezing, runny nose, eye itch, and unrefreshed sleep. Postnasal drip and sinus pain were not significantly changed.

The results show evidence that acupuncture modulates immune responses in adults with moderate to severe PAR. These effects include reduction in dust mite-specific IgE and downregulation of substance P, occurring along with improvements in symptoms and quality of life. The findings may be relevant to the study of acupuncture for asthma and other allergic diseases.

COMMENT: There is increasing interest in treatments other than traditional medicine for atopic disease. This study is the first to report a decrease in total IgE, as well as house

dust mite-specific IgE, after acupuncture in patients with PAR. This is a study that we can refer to when our patients ask about the use and efficacy of alternative treatment options for PAR. Since the study excluded patients with asthma, future studies in patients with other forms of atopic disease may further elucidate the benefit of acupuncture.

V.H.-T.

McDonald JL, Smith PK, Smith CA, et al: Effect of acupuncture on house dust mite specific IgE, substance P, and symptoms in persistent allergic rhinitis. Ann Allergy Asthma Immunol. 2016;116:497-505.

Keywords: allergic rhinitis, complementary and alternative medicine, house dust mite

Asthma Linked to Altered Platelet Properties

Asthma is associated with an increased risk of pulmonary embolism but not deep vein thrombosis, suggesting that activation of coagulation may not be the relevant mechanism. Clot retraction and other factors involved in the clotting process were assessed in patients with allergic asthma.

The study included 81 patients with allergic asthma, 41 steroid-naive and 40 steroid-treated, along with 50 healthy controls. On thromboelastometry, slightly activated coagulation was found only in steroid-treated asthma patients. Asthmatic subjects showed a significant reduction in the rate of clot retraction—the final step of coagulation and a primary step in thrombus clearance. Asthma was also associated with a higher clot volume at 40 minutes and increased lactate production in retracting clots, in addition to higher exhaled NO, decreased FEV_1, and elevated blood eosinophil count.

On analysis including asthmatic subjects and controls, the clot retraction rate (CRR) was positively correlated with the results of spirometry but negatively correlated with exhaled NO, blood eosinophil count, and lactate production. However, on analysis of steroid-treated asthma patients, the CRR was unrelated to exhaled NO and blood eosinphils. Across groups, lactate production was negatively correlated with FEV_1 and positively correlated with exhaled NO.

The results suggest that asthma is associated with inhibition of the CRR, which might predispose to pulmonary embolism. If platelets are less able to generate contractile force, thrombi may be less stable and more likely to embolize. The authors note that current antithrombotic and antiplatelet drugs would not normalize clot retraction.

COMMENT: The authors found that individuals with asthma have reactive nitrogen species that diminish platelet contractility and CRR through a decrease in platelet energy production. This intriguing observation deserves further study, but it could help explain why asthmatic patients have an increased risk of pulmonary embolism.

C.C.R.

Tomiasiak-Lozowska MM, Rusak T, Misztal T, et al: Reduced clot retraction rate and altered platelet energy production in patients with asthma. J Asthma. 2016;53:589-598.

Keywords: asthma (adult), pulmonary embolism

REVIEWS OF NOTE

COMMENT: Clinicians are torn regarding the utility/benefits versus risks of e-cigarettes as a smoking cessation aid in adult smokers, as nicely enunciated by Yeh, Bullen and Glantz in an interactive "Clinical Decisions" article. Meanwhile, the dramatic uptick in the use of these products continues to cause unexpected consequences in a vulnerable population: namely, children and youth. The explosion in the use of e-cigarettes has been unfortunately accompanied by a concomitant explosion in the number of calls to the poison control center, with most incidents occurring in young children attracted to the appealing e-liquid containers and packaging. Also, the nagging fear among pediatricians that use of e-cigarettes may result in an increased initiation of traditional cigarette and combustible tobacco product use by never-smoking teenagers transitioning into adulthood was recently affirmed in a prospectively followed cohort in Southern California.

C.D.

Yeh JS, Bullen C, Glantz SA: E-cigarettes and smoking cessation. N Engl J Med. 2016;374:2172-2174

Kamboj A, Spiller HA, Casavant MJ, et al: Pediatric exposure to e-cigarettes, nicotine, and tobacco products in the United States. Pediatrics. 2016;137:e20160041.

Barrington-Trimis JL, Urman R, Berhane K, et al: E-cigarettes and future cigarette use. Pediatrics.2016;138:e20160379.

COMMENT: This article provides an update on the pathophysiology and comorbidities associated with COPD.

B.E.C.

Marchetti N, Criter GJ: Update in chronic obstructive pulmonary disease 2015. Am J Respir Crit Care Med. 2016;193:1092-1100.

COMMENT: This editorial is particularly helpful in focusing on the role of biologics in a group of patients previously thought to have primarily COPD. Significant eosinophilic airway inflammation is the primary determinant.

B.E.C.

Pavord ID, Agusti A: Blood eosinophil count: a biomarker of an important treatable trait in patients with airway disease. Eur Respir J. 2016;47:1299-1303.

COMMENT: This is an update of the EAACI/GA^{2}LEN consensus statement on chronic inducible urticarias. The expert panel shares the latest changes in the diagnosis and management of these illnesses.

J.J.O.

Magerl M, Altrichter S, Borzova E, et al: The definition, diagnostic testing, and management of chronic inducible urticarias–the EAACI/GA^{2}LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016;71:780-802.