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FEATURE ARTICLES

Should the LABA Black Box Be Removed?

Long-acting beta-agonists (LABAs) have been linked to increased in asthma-related deaths in adults and asthma-related hospitalizations in children. A previous meta-analysis suggested that concomitant inhaled glucocorticoids offset the LABA-associated increase in pediatric hospitalizations. This prospective trial evaluated a fixed-dose combination of salmeterol and fluticasone propionate for safety in children.

The study included 6,208 children, aged 4 to 11, who were taking daily asthma medications and had one or more exacerbations in the previous year. They were randomly assigned to 6 months of fluticasone-salmeterol or fluticasone alone. The main safety endpoint was time to first serious asthma-related event.

There were 48 serious asthma-related events, all hospitalizations: 27 with fluticasone-salmeterol and 21 with fluticasone only. The difference was within the specified limits of noninferiority. On efficacy analysis, asthma exacerbations occurred in 8.5% of children with fluticasone-salmeterol versus 10% with fluticasone alone. This difference was also nonsignificant.

The trial adds new evidence that a fixed-dose fluticasone-salmeterol combination does not increase serious asthma-related events in children with persistent asthma. The results of the secondary efficacy analysis highlight the need for more research on factors affecting exacerbation risk after stepping down from combination therapy. The authors note the short duration of the trial and the low rate of serious asthma-related events.

Keywords: asthma (child), LABAs, safety

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- 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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There is concern about the safety risks of combined long-acting beta-agonists (LABAs) and inhaled glucocorticoids for asthma treatment. The authors report an FDA-mandated postmarketing safety study comparing serious adverse events with a budesonide-formoterol combination versus budesonide alone.

The multicenter randomized trial included 11,693 patients, aged 12 years or older, with persistent asthma. All were taking daily asthma medications and had one to four exacerbations in the previous year; patients with a history of life-threatening asthma were excluded.

Patients were assigned to 26 weeks on budesonide-formoterol or budesonide alone. Time to first serious asthma-related event—a composite of death, intubation, and hospitalization—was compared between groups. Time to first asthma exacerbation was assessed as a secondary efficacy outcome.

The noninferiority study found no significant difference in serious asthma-related events: 43 patients with budesonide-formoterol and 40 with budesonide only. Two patients in the budesonide-formoterol group died of asthma-related causes; one of these also had asthma-related intubation. On efficacy analysis, budesonide-formoterol was associated with a fewer asthma exacerbations: hazard ratio 0.84.

For adolescents and adults with persistent, mainly moderate-to-severe asthma, budesonide-formoterol does not increase serious asthma-related events, compared to budesonide only. There is evidence of a reduced asthma exacerbation rate in the budesonide-formoterol group. Pooled analysis of the four FDA-requested studies will be performed when all data are available.

COMMENT: These two FDA-mandated, large-scale noninferiority studies compared budesonide-formoterol and fluticasone-salmeterol to their respective single-agent steroid in children and adults with asthma. The results convincingly show that the risk of serious events was no different between the treatments, with at least 95% certainty. The strengths of these trials are the well-thought out study designs, large numbers of patients, and reassuringly low numbers of adverse events. While these were not designed to be efficacy studies, they add to the body of evidence regarding the potential benefits (such as the BADGER study by Lemanske et al) versus the low likelihood of risks associated with use of fixed-dose ICS-LABA combination, for patients whose asthma is uncontrolled on low-dose inhaled steroids.

C.D.

Peters SP, Bleecker ER, Canonica GW, et al: Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med. 2016;375:850-860.

Stempel DA, Szefler SJ, Pederson S, et al: Safety of adding salmeterol to fluticasone propionate in children with asthma.
N Engl J Med. 2016;375:840-849.

Keywords: asthma (adult), LABAs, safety

Maternal and Infant Vitamin D Supplementation– Will It Put Us Out of Business?

Previous reports have suggested that maintaining normal vitamin D status during early life might prevent the development of atopy. This randomized trial evaluated the impact of vitamin D supplemen- • • •

tation during pregnancy and infancy on the risk of allergic sensitization in early childhood.

Pregnant women in New Zealand and their infants were randomly assigned to receive supplemental vitamin D, in lower or higher doses, or placebo. From 27 weeks' gestation to delivery, the mothers received vitamin D 1,000 or 2,000 IU or placebo; from birth to age 6 months, the infants received vitamin D 400 or 800 IU or placebo. At 8 months, the children underwent measurement of serum-specific IgE antibodies. The two groups were also compared for rates of primary care visits for various respiratory diagnoses, including asthma.

The analysis included specific IgE measurements in 185 of 260 children. Sensitization rates were significantly different for four dust mite antigens. For Der-f1, sensitization rates were 18% with placebo, 10% with lower-dose vitamin D, and 2% for higher-dose vitamin D. Respective values were 14%, 3%, and 2% for Der-f2; 19%, 14%, and 3% for Der-p1; and 12%, 2%, and 3% for Der-p2. The number of mite antigens and the magnitude of IgE response to these antigens were both significantly lower in the vitamin D groups.

Primary care visits for asthma were reported for 11% of children in the placebo group, none in the lower-dose vitamin D group, and 4% in the higher-dose vitamin D group. There were no significant differences in visits for other reasons, including colds, upper respiratory infections, or bronchiolitis.

Maternal and infant vitamin D supplementation reduces dust mite sensitization at age 18 months. Maintaining normal vitamin D status may also reduce primary care visits for asthma. Longer follow-up will be needed to confirm the effect on asthma prevalence.

COMMENT: This prospective study found that vitamin D supplementation during pregnancy and infancy translated into decreases in dust mite sensitivity and primary care visits for the diagnosis of asthma. As the authors note, we do not know if the protection demonstrated at age 18 months will be maintained in later life. Certainly, a firmer diagnosis of asthma can be made in older children. Several recent studies (Rothers J, et al: J Allergy Clin Immunol. 2011;128:1093-1099 and Weisse K, et al: Allergy 2013;68:220-222) have demonstrated that high as well as low cord blood 25(OH)D concentrations are associated with an increased risk of aeroallergen sensitization at age 5, and that higher maternal 25(OH)D concentration during late pregnancy is associated with an increased risk of food allergen sensitization at age 2. Only time will tell if this apparent protection will remain.

J.J.O.

Grant CC, Crane J, Mitchell EA, et al: Vitamin D supplementation during pregnancy and infancy reduces aeroallergen sensitization: a randomized controlled trial.
Allergy. 2016;71:1325-1334.

Keywords: asthma (child), pregnancy, prevention, vitamin D

Phenotyping Refractory Asthma in Children: A New Approach

There is no standard assessment of response to systemic corticosteroids in children with severe therapy-resistant asthma (STRA). A previous study showed that children with STRA are heterogeneous in terms of lung function, inflammatory markers, and airway remodeling. The authors evaluated a multidomain approach to assessing steroid responsiveness in pediatric STRA.

The study included 82 children and adolescents, median age 12 years, with STRA. Each received a clinically indicated intramuscular dose of triamcinolone. Before and 4 weeks after treatment, patients were evaluated using a multidomain definition of steroid responsiveness, incorporating changes in symptoms (based on the Asthma Control Test), spirometry, and inflammatory markers. Patterns of response were analyzed, attempting to identify predictors of systemic steroid responsiveness.

Forty-three percent of children were classified as having a symptom response, while 54% had a lung function response. On analysis of inflammatory markers, response rates were 52% for exhaled nitric oxide and 54% for sputum eosinophils.

No reliable predictors of response were identified. Seventy-two percent of children responded in at least one domain, but only 13% responded in all domains. Fifteen percent did not respond in any domain.

The multidomain evaluation confirms the variable response to systemic corticosteroid among pediatric patients with STRA. None of the clinical and inflammatory features analyzed can predict the steroid-response pattern. The authors suggest that individual response patterns might be a useful guide to selecting add-on therapies.

COMMENT: Severe therapy-resistant asthma in children is very difficult to control despite regular controllers and occasional systemic corticosteroids. This study monitored the domains of symptoms, lung function, and inflammation in 54 children with STRA after IM triamcinalone. Interestingly, symptoms improved in only 43% of patients, whereas 54% had improvement in lung function. Exhaled NO improved in 52% and sputum eosinophils in 53%. The authors suggest that phenotypic differences could be responsible for the variation in responses. This multidomain assessment model could be useful for predicting responses to various "add-on" biologics as they become available.

S.M.F.

Bossley CJ, Fleming L, Ullmann N, et al: Assessment of corticosteroid response in pediatric patients with severe asthma by using a multidomain approach.
J Allergy Clin Immunol. 2016;138:413-420.

Keywords: asthma (child), severe asthma, steroid responsiveness

Dupilumab Phase 2b for Asthma Does Not Disappoint!

The new monoclonal antibody dupilumab blocks both interleukin (IL)-4 and IL-13. In a phase 2a trial, it showed efficacy in patients with persistent, moderate to severe asthma and ongoing Th2 inflammation. This phase 2b trial evaluated the use of add-on dupilumab in patients with uncontrolled persistent asthma at differing blood eosinophil counts.

The multicenter, randomized, double-blind trial included 769 adults with persistent asthma that was uncontrolled despite medium- to high-dose inhaled corticosteroids plus a long-acting beta-2 agonist. Four groups received dupilumab, 200 or 300 mg every 2 or 4 weeks, while a fifth group received placebo. Treatment continued for 24 weeks. The main efficacy outcome was 12-week change in FEV_1 among the subgroup (325 patients) with a baseline blood eosinophil count of at least 300 eosinophils/μL. Safety outcomes were evaluated as well.

In patients with a blood eosinophil count of 300/μL or greater, FEV_1 increased (compared to placebo) by 0.21 L with dupilumab 200 mg every 2 weeks and by 0.26 L with dupilumab 300 mg every 3 weeks. Comparable changes in FEV_1 were observed in the overall study sample as well as in the group with a baseline blood eosinophil count of less than 300 eosinophils/μL. The improvements in FEV_1 subgroup persisted through 24 weeks.

Dupilumab every 2 weeks also produced the largest decreases in annualized exacerbation rates: by 70.0% to 70.5% in the overall sample, 71.2% to 80.7% in patients with a blood eosinophil count of at least 300/μL, and 59.9% to 67.6% in those with a blood eosinophil count of less than 300/μL. Upper respiratory infections and injection site reactions were more frequent with dupilumab compared to placebo.

Treatment with dupilumab increases FEV_1 while reducing exacerbation risk in patients with uncontrolled persistent asthma. These benefits are achieved even in patients with a baseline eosinophil count of less than 300/μL. Add-on dupilumab could be a safe and effective treatment for patients with uncontrolled persistent asthma.

COMMENT: Many have been excited to see the data regarding dupilumab for asthma. This fully human anti-IL4 receptor-alpha monoclonal antibody blocks IL-4 as well as IL-13 signaling. Thus from a basic science perspective, it should have added efficacy through its blockade of two Th2 signaling endpoints. This phase 2b trial does not disappoint, with a statistically significant increase in FEV_1 by week 12 that remained so through week 24. Dupilumab also reduced annualized exacerbation rates, in a group of patients already receiving moderate- to high-dose inhaled corticosteroids plus long-acting beta-2 agonist. What is somewhat surprising is these results were independent of baseline eosinophil count.

J.J.O.

Wenzel S, Castro M, Corren J, et al: Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016;388:31-44.

Keywords: asthma (adult), biologics, dupilumab

FOCUS ON THE HYGIENE HYPOTHESIS

Thumbs Up for Nail-Biting

If early-life exposure to microbes affects allergy risk, then common childhood habits like thumb-sucking and nail-biting might have significant effects. This theory was evaluated in a population-based birth cohort with follow-up into adulthood.

The Dunedin Multidisciplinary Health and Development Study included 1,037 infants born in that New Zealand city in 1972-73. Parental questionnaires included items about thumb-sucking and nail-biting when the children were 5 to 11 years old. The participants underwent skin-prick testing at age 13 and 32; those with a 2 mm or larger wheal response to at least one common allergen were considered to have atopic sensitization. Associations between childhood habits and later atopic sensitization, asthma, and hay fever were assessed, with adjustment for confounders.

Parents reported that 31 percent of children were frequent thumb-suckers or nail-biters at some time. These children were less likely to develop atopic sensitization, either at age 13 or 32 years: odds ratio 0.67 and 0.61, respectively. The associations remained significant on adjusted analysis.

Atopy risk was even lower for participants with both childhood habits. However, nail-biting and thumb-sucking were unrelated to the risk of asthma or hay fever, either in adolescence or young adulthood.

The childhood habits of thumb-sucking and nail-biting may be associated with a lower risk of atopic sensitization later in life. While these results may support the hygiene hypothesis, the lack of association with asthma or hay fever is unexplained.

COMMENT: Another study on the hygiene hypothesis—this time from New Zealand. It suggests that children who sucked their thumbs or bit their nails between age 5 and 11 were less likely to have atopic sensitization at age 13. The effect persisted until adulthood, with an even greater risk reduction for those who engaged in both habits. Inexplicably, no association was found with asthma or hay fever. The key recall question posed to parents was ambiguous in its wording and interpretation, and the lack of effect on development of allergic rhinitis/asthma does not make sense. Yet the findings are similar to the study by Hesselmar et al (Pediatrics. 2013;131:e1829-1837), which found that sucking a pacifier resulted in a population less likely to develop allergies.

C.D.

Lynch SJ, Sears MR, Hancox RJ: Thumb-sucking, nail-biting, and atopic sensitization, asthma, and hay fever.
Pediatrics. 2016;138:e20160443.

Keywords: atopy, hygiene hypothesis, prevention

Contact with Farm Animals May Explain Lower Asthma Risk in Amish

Although the Amish and Hutterites are both agrarian societies, they differ substantially in childhood asthma prevalence: approximately 5% for Amish versus 20% for Hutterite children. The Amish follow traditional agricultural practices, while the Hutterites use industrialized farming techniques. This study compared exposures, immune responses, and asthma risk for Amish and Hutterite farm children.

The study included matched groups of 30 Amish children in Indiana and 30 Hutterite children in South Dakota. The two groups followed similar lifestyles and had similar genetic ancestry. None of the Amish children had asthma, compared to 20% of the Hutterite children. Specific IgE measurements showed a substantially lower rate of allergic sensitization in the Amish children.

Median house dust endotoxin levels were 6.8-fold higher in Amish homes. There were also significant differences in microbial composition between the Amish and Hutterite homes. Studies of immune profiles showed major differences in innate immune cell proportions, phenotypes, and function. In a mouse model of allergic asthma, airway hyperreactivity and eosinophilia were inhibited by dust extracts from Amish but not Hutterite homes.

The very low risk of asthma in Amish compared to Hutterite children may reflect differences in household microbial exposures and in the activation of innate immune signaling. Neutrophils, eosinophils, and monocytes may be the major cellular targets of these environmental exposures. Further understanding of the relevant stimuli and innate immune pathways may lead to new strategies for asthma prevention.

COMMENT: It is puzzling that while the Amish and the Hutterites both originated in Europe, share the same genetic ancestry, and are farming communities with similar beliefs, they have differing rates of asthma. In this fascinating and nuanced study, Stein and colleagues discovered a novel reason for this discrepancy. The Amish exhibit a strong innate immune response, driven by the lipopolysaccharide on the cattle in the barns that they frequent. The Hutterites lack that protective response, attributable to their lifestyle of industrialized communal farm living and physical separation from farm animals. While this study could have benefited from having larger numbers of subjects, including a few Amish children with asthma (there were none), it does add weight to the hygiene hypothesis. As pointed out by Chatila in an insightful editorial (N Engl J Med. 2016;375:477-479), the question of when and how often exposure to farm dust might be needed to protect children remains to be determined.

C.D.

Stein MM, Hrusch CL, Gozdz CL, et al: Innate immunity and asthma risk in Amish and Hutterite farm children.
N Engl J Med. 2016;375:411-421.

Keywords: asthma (child), farm environment, hygiene hypothesis

Household Environmental Controls Come Up Short

Indoor allergens are important contributors to asthma morbidity, perhaps especially in the inner-city. Individual environmental control measures are part of current asthma management guidelines, but their effectiveness is debatable. This study evaluated a multifaceted environmental intervention for asthma patients in New York City.

The randomized controlled trial included adults and children with asthma who were sensitized and exposed to one or more indoor allergens. After optimized asthma controller therapy, 125 patients were assigned to receive an individualized household allergen reduction intervention, including educational modules targeting specific allergens. One hundred twenty-two controls received a sham intervention. The main outcome of interest was reduction in the need for asthma medication at 40 weeks.

The intervention group had reduced exposure to all measured allergens: cat, dog, dust mite in bedroom, and cockroach and mouse in kitchen and bedroom. Controls had reductions in dust mite, mouse allergen in bedroom, and cockroach allergen in kitchen. Both groups had reductions in National Asthma Education Prevention Program-based therapy: from step 3.5 to 4.4 in the intervention group and from step 4.4 to 3.4 in the control group. Other asthma outcomes were also similar between groups, including asthma symptom days, lung function measures, and IgE levels.

The multifaceted intervention evaluated in this trial successfully reduced indoor allergen exposure for inner-city asthma patients. However, allergen reduction did not affect the need for asthma medications or improve other asthma outcomes. Further study is needed to inform the recommendations for allergen avoidance in asthma.

COMMENT: This fascinating study examined whether "multifaceted indoor avoidance measures" could reduce asthma pharmacologic therapy. The active treatment group had significant reductions in measured levels of cat, dog dust mites, cockroach, and mouse allergen, but no accompanying reduction in asthma therapy. This is obviously not the outcome we had hoped for. However, as pointed out by Dr. Eggleston's accompanying editorial (J Allergy Clin Immunol Pract. 2016;4:680:681), it is important to consider that the control group did indeed demonstrate reduction in several

indoor allergen levels, and thus it becomes difficult to tease out the comparative effect between groups. Likewise, one must consider that intermittent exposure to allergens (which could be prolonged) also occurs when the subjects leave their homes. This is certainly not an easy topic to study, but more research is sure to come.

J.J.O.

DiMango E, Serebrisky D, Narula S, et al: Individualized household allergen intervention lowers allergen level but not asthma medication use: a randomized controlled trial.
J Allergy Clin Immunol Pract. 2016;4:671-679.

Keywords: allergen avoidance, asthma (adult), asthma (child), inner-city

FOCUS ON DRUG ALLERGY

Specific IgE in Drug Anaphylaxis: It's All in the Timing

Chlorhexidine is a widely used disinfectant that can cause severe allergic reactions. Specific IgE to chlorhexidine is highly sensitive and specific within 6 months of a reaction, but its performance over longer time periods is unknown. This follow-up study evaluated the dynamics of specific IgE in patients with chlorhexidine allergy, including re-exposed patients.

Forty-four patients were diagnosed with chlorhexidine allergy at a Danish anesthesia allergy center from 1999 to 2015. Of these, 23 participated in the analysis, which included blood samples drawn at the time of the reaction and prospective samples obtained during follow-up.

Most patients had anaphylactic reactions to chlorhexidine. Specific IgE was measured within hours of the reaction in 8 patients, and exceeded 0.35 kUA/L in 6 of them. On allergy testing 2 to 4 months later, 22 of 23 patients had specific IgE greater than 0.35 kUA/L. During follow-up, specific IgE dropped below this level in 17 of 23 patients, in some cases within as little as 4 months.

Seven patients were re-exposed to chlorhexidine on nine occasions. In most cases, re-exposure caused repeat symptoms and increased specific IgE levels. In two cases, symptoms occurred on re-exposure in patients with specific IgE of less than 0.35 kUA/L.

For patients with chlorhexidine allergy, specific IgE levels may change over time. The optimal time to detect specific IgE greater than 0.35 kUA/L appears to be after 1 month but less than 4 months after exposure. Chlorhexidine re-exposure is common, and can cause symptoms even in patients with specific IgE less than 0.35 kUA/L.

COMMENT: Few studies have evaluated specific IgE to drugs over time. This longitudinal study followed up patients with perioperative chlorhexidine anaphylaxis. At the time of anaphylaxis, all patients had elevated specific IgE. However, the levels declined relatively quickly, with many patients having negative tests after only 4 months. Despite negative tests, some of these patients still reacted. Whether skin testing would have picked up these false negatives is unclear.

D.A.K.

Opstrup MS, Poulsen LK, Malling HJ, et al: Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. Clin Exp Allergy. 2016;46:1090-1098.

Keywords: anaphylaxis, drug allergy, specific IgE

Perioperative Drug Allergy Workups Have Low Yield

Most of what is known about perioperative drug hypersensitivity reactions (HSRs) comes from retrospective studies. The most common agents responsible for HSRs vary between countries. This study reports a prospective experience with a comprehensive management plan for perioperative HSRs.

The authors carried out their comprehensive allergy evaluation plan for perioperative HSRs in 25 patients at a Boston teaching hospital over a 17-month period. The plan included a standardized skin testing protocol performed within 6 months, along with data on the characteristics of the HSR and other patient information.

The patients were 13 females and 12 males, median age 52 years. Reactions were cutaneous in 68% of patients, cardiovascular in 64%, and pulmonary in 24%. A culprit drug, defined as a positive skin test result, was identified for 9 patients. In 6 of these patients, the implicated drug was cefazolin. Seven of eight patients were able to tolerate subsequent anesthesia after the comprehensive evaluation and management plan. In five patients, an alternative antibiotic was used.

The analysis suggests that antibiotics are the main cause of perioperative HSRs. Skin testing performed within 6 months may improve the rate of positive results, but in most cases no culprit drug is identified. Within comprehensive evaluation, most patients can tolerate subsequent anesthesia.

COMMENT: This prospective study relied on a comprehensive allergy evaluation plan in patients suffering from perioperative HSRs. The investigators found that antibiotics (specifically cefazolin) were the most likely cause of a reaction. Interestingly, a cause was ultimately found for only 36% of patients. Ability to identify the cause was hampered by lack of reliable skin test protocols beyond penicillin and concern that even a 6-month delay may have resulted in false-negative results, as a result of waning skin test positivity. In the end, the vast majority of patients who underwent a later anesthetic procedure were able to tolerate it without reaction. The authors are to be applauded for their study • • •

and the added information it provides regarding perioperative HSRs.

J.J.O.

Kuhlen JL Jr, Camargo CA Jr, Balekian DA, et al: Antibiotics are the most commonly identified cause of perioperative hypersensitivity reactions.
J Allergy Clin Immunol Pract. 2016;4:697-704.

Keywords: antibiotics, drug allergy, skin testing

Can We Safely Diagnose Delayed Drug Hypersensitivity in Children?

Recent studies have reported promising results with T cell proliferation and cytokine release assays for in vitro diagnosis of drug hypersensitivity reactions (DHRs). There are few data on the use of these assays in children. The authors compared the lymphocyte proliferation assay and combination cytokine assays for diagnosis of DHRs in the pediatric population, during the acute and postrecovery phases.

The study included 16 children and adolescents with clinically diagnosed DHRs. A total of 18 in vitro tests were performed, including drug-specific lymphocyte proliferation assays (LPAs) and interferon (IFN)-γ and interleukin-4 (IL-4) assays. Seven patients were tested in the acute phase of DHR, 7 after recovery, and 2 in both phases.

During the acute phase, the lymphocyte proliferation assay appeared to offer higher sensitivity. However, the cytokine assays had a higher rate of drug-specific responses during both phase: in the acute phase, 77.8% with LPA, 88.9% with IFN-γ, and 100% with IL-4. In the postrecovery phase, the rates were 33.3%, 66.7%, and 66.7%, respectively. The combination of the two cytokine assays produced the highest rate of positive drug-specific responses in both phases.

The results support the use of in vitro T cell proliferation and cytokine release assays for diagnostic evaluation of children with DHRs. The IFN-γ and IL-14 assays offer higher diagnostic utility than LPAs, particularly in combination. These rapid in vitro tests may be a significant advance in the management of pediatric DHR.

COMMENT: The frustration of diagnosing non-IgE-mediated drug reactions cannot be underestimated. The authors give us hope that the use of in vitro cytokine assays—with sensitivity of 100% in the acute reaction phase and 83% in the postrecovery phase—may aid in improving diagnosis of these reactions. Advantages include safety, without the risk of exposure, and turnaround in less than 24 hours. These assays are an exciting and promising alternative for our patients with delayed-type drug hypersensitivity reactions.

V.H.-T.

Haw WY, Pola KE, McGuire C, et al: In vitro rapid diagnostic tests for severe drug hypersensitivity reactions in children.
Ann Allergy Asthma Immunol. 2016;117:61-66.

Keywords: drug hypersensitivity reactions, in vitro testing

Does Specific Immunotherapy Really Improve Atopic Dermatitis?

Although specific immunotherapy (SIT) is a mainstay of treatment for allergic disease, its role in the treatment of atopic dermatitis (AD) remains unclear. A Cochrane systematic review of the efficacy and safety of SIT for treatment of AD is reported.

The review identified 12 randomized controlled trials of SIT using standardized allergen extracts for the treatment of AD in sensitized patients. The studies included a total of 733 patients. Type of SIT was subcutaneous in six studies, sublingual in four, and oral and intradermal in one each. Ten trials treated patients sensitized to house dust mite. The studies had a moderate risk of bias, with high loss to follow-up and concerns about blinding. Study heterogeneity limited the ability to perform meta-analysis.

Analysis of three studies including 208 patients showed no significant effect of SIT on patient-reported global disease severity or eczema symptoms (the primary outcomes). Data from two studies including 85 patients found significant improvement in global disease severity, risk ratio 2.85; and reduction in itching, with a mean difference of 4.20 on a 10-point scale. Six studies including 262 patients suggested a significant researcher-rated improvement in eczema severity: risk ratio 1.48.

Within the limitations of the available data, the review provides little support for the use of SIT to treat AD. Higher-quality studies are needed to clarify the true value of allergen immunotherapy for this common condition.

COMMENT: Sadly, the authors were unable to demonstrate evidence that SIT is effective for treating atopic eczema when examining the primary outcomes of patient-reported global disease severity improvement and eczema symptoms mean difference. The researchers highlight that their meta-analysis was limited due to extreme statistical heterogeneity. They conclude by calling for further research to determine whether SIT really has a role in the treatment of atopic eczema.

J.J.O.

Tam HH, Calderon MA, Manikam L, et al: Specific allergen immunotherapy for the treatment of atopic eczema: a Cochrane systematic review.
Allergy.2016;71:1345-1356.

Keywords: atopic dermatitis, Cochrane review, specific immunotherapy

Adrenaline Autoinjector Prescriptions and Use in Australian Schools

In Australia, prescription of adrenaline autoinjectors (AAIs) has increased faster than rates of food allergy, raising concerns about AAI overprescribing. In 2008, the state of • • •

Victoria enacted legislation requiring schools to develop anaphylaxis management plans. This study evaluated trends in the prevalence of schoolchildren at risk of anaphylaxis and the use of AAIs in school settings.

The researchers analyzed Victoria statewide surveys from more than 1,500 government schools including data on more than 500,000 children per year from 2009 to 2014. Trends in the prevalence of children at risk of anaphylaxis (diagnosed or reported) were analyzed, along with annual rates of AAI use in the school environment.

The prevalence of schoolchildren at risk of anaphylaxis increased from 0.98% in 2009 to 1.38% in 2014. Prevalence of anaphylaxis risk decreased between the final year of primary school and the first year of secondary school, possibly reflecting a change in parental reporting of risk. In each year, the number of AAI activations was between 6 and 8 per 1,000 students at risk of anaphylaxis. Use of AAIs was substantially higher in secondary versus primary schools.

The data suggest a rising prevalence of anaphylaxis risk among schoolchildren in Victoria, Australia. At a time of increased AAI prescribing, the activation rate is stable, suggesting that AAIs are being either overprescribed or underused. The study documents changes in anaphylaxis risk reporting between primary and secondary school.

COMMENT: The government of Victoria, Australia legislated anaphylaxis management plans for schools in 2008. The prevalence of anaphylaxis increased by 41% from 2009 to 2014. The use of AAIs was much greater in urban compared to rural schools. Interestingly, the number of students in primary schools at risk for anaphylaxis was greater than for students in secondary schools, which may have been a reporting phenomenon. This might also explain why the use of AAIs in secondary schools was greater per child at risk than for primary school students. The authors note that there may have been overprescribing of AAIs, since through the years the activation rate was relatively constant while the prescription rates increased. However, this could also be explained by potential underutilization.

S.M.F.

Loke P, Koplin J, Beck C, et al: Statewide prevalence of school children at risk of anaphylaxis and rate of adrenaline autoinjector activation in Victorian government schools, Australia.
J Allergy Clin Immunol. 2016;138:529-535.

Keywords: anaphylaxis, epinephrine, food allergy

Might CpG-Coated Nanoparticles Make Peanut OIT Safer?

Although peanut oral immunotherapy (OIT) has promising clinical effects, the risk of adverse events appears unacceptably high. This study evaluated an approach using CpG-coated poly (lactic-co-glycolic acid) nanoparticles (CpG/PN-NPs) containing peanut extract in a mouse model of peanut allergy.

Experiments were performed in peanut-sensitized C3H/HeJ mice. The animals received four weekly gavage treatments with CpG/PN-NPs, vehicle, nanoparticles alone, peanut alone, CpG nanoparticles, or peanut nanoparticles. Treatment was followed by a series of five monthly oral peanut challenges, with assessment of hypersensitivity and immunologic reactions.

Active treatment with CpG/PN-NPs provided good protection against anaphylactic reactions to peanut challenge. In addition to lower symptom scores and reduced change in body temperature, the CpG/PN-NP-treated mice had a lesser increase in plasma histamine response, compared to all other treatment groups. The CpG/PN-NP OIT group also had a lasting decrease in peanut-specific IgE/IgG_1 with an increase in peanut-specific IgG_{2a}. Studies in splenocyte cultures suggested that CpG/PN-NPs reduced Th2 cytokines, including interleukin (IL)-4, IL-5, and IL-13, while increasing interferon-γ.

This experimental study describes a promising new approach to peanut OIT using CpG/PN-NPs containing peanut extract. The results suggest long-term protection against anaphylaxis with a good safety profile, with reduced peanut-specific Th2 responses and increased Th1 responses.

COMMENT: These researchers used CpG-coated nanoparticles containing peanut extract to deliver OIT in peanut-allergic mice. Just four weekly oral doses provided protection from anaphylaxis after repeated peanut challenges for over 4 months after last treatment dose. The nanoparticle treatments had an impressive safety profile and produced strong immune responses, suggesting that peanut/CpG nanoparticles could have potential benefit in humans.

S.M.F.

Srivastava KD, Siefert A, Fahmy TM, et al: Investigation of peanut oral immunotherapy with CpG/peanut nanoparticles in murine model of peanut allergy.
J Allergy Clin Immunol. 2016;138:536-543.

Keywords: nanoparticles, oral immunotherapy, peanut allergy

Sure, Use the Acetaminophen or Ibuprofen

Observational data have suggested that acetaminophen use might be associated with increased asthma morbidity in children. This has led some physicians to recommend avoiding acetaminophen in children with asthma. This randomized trial compared the effects of acetaminophen versus ibuprofen in young children with mild persistent asthma.

The multicenter trial included 300 US children, aged 1 to 6 years, with mild persistent asthma. Children were randomly assigned to take acetaminophen or ibuprofen, as indicated for treatment of fever or pain, for 48 weeks. Rates of asthma morbidity—exacerbations or need for systemic gluco- • • •

corticoid therapy—were compared between groups. All children received standardized asthma controller medications as part of a simultaneous trial.

The children received a median 5.5 doses of their assigned analgesic medication, with no difference between groups. Asthma morbidity was also similar between groups: mean number of asthma exacerbations was 0.81 per children with acetaminophen and 0.87 with ibuprofen. Percentages of children with one or two exacerbations were similar as well. Secondary outcomes were also similar between groups, including percentage of days with controlled asthma, albuterol use, unscheduled healthcare use, and adverse events.

This randomized trial finds no difference in asthma morbidity or control for young children with mild persistent asthma taking as-needed acetaminophen versus ibuprofen. The results help to answer an important practical question regarding routine treatment of fever or pain in children with asthma.

COMMENT: Recent studies have raised the concern that acetaminophen use may lead to the development of asthma in otherwise healthy children. While this study does not answer that unsettling question, it does help provide reassurance that as-needed use of acetaminophen or ibuprofen in children with mild persistent asthma does not worsen asthma or wheezing. Predictably, children with asthma exacerbations tended to use more acetaminophen or ibuprofen, presumably since viral infections (and concomitant fever and myalgia) are triggers of exacerbations, and not the other way around. Having a placebo arm (withheld for ethical reasons) would have helped close the lid on the case.

C.D.

Sheehan WJ, Mauger DT, Paul IM, et al: Acetaminophen versus ibuprofen in young children with mild persistent asthma. 2016;375:619-630.

Keywords: acetaminophen, asthma (child)

Early-Onset Asthma Is Bad Enough without Smoking

Persistent asthma and tobacco smoking are both associated with an increased risk of irreversible airflow obstruction. These two risk factors are often assumed to interact, although this has never been confirmed in prospective studies of children with persistent asthma. The interactive effects of smoking and asthma on risk of airflow obstruction were evaluated in a birth cohort with follow-up into adulthood.

The analysis included 840 subjects from the Dunedin Study, with follow-up from birth to age 38 years. Based on parent and participant reports at different ages, 91 subjects were classified as having childhood-onset persistent asthma 93 with late-onset asthma, and 85 with asthma in remission. The remaining 572 subjects were classified as nonasthmatic. Cumulative smoking history and lung function parameters were assessed from age 18 to 38 years.

Childhood asthma did not affect subsequent smoking history—about half of subjects with childhood asthma and half of those without asthma had ever smoked. Both smoking history and childhood-onset persistent asthma were associated with reduced FEV_1/FVC ratios at age 38.

However, the associations differed by asthma phenotype. Smoking was linked to reduced pre- and post-bronchodilator FEV_1/FVC ratios for the late-onset or asthma in remission phenotypes, and in the nonasthmatic group. In contrast, smoking did not affect the risk of reduced lung function in those with childhood-onset persistent asthma.

This longitudinal study confirms the increased risk of airflow obstruction in adults with a history of persistent childhood asthma, but shows no additional increase in risk based on smoking history. The results show no evidence that smoking and persistent childhood asthma has additive or multiplicative effects on the risk of irreversible airflow obstruction at age 38. The researchers note that significant effects of smoking may become more apparent later in life.

COMMENT: This study may seem counterintuitive, but it is an important contribution to the literature. One-third of participants with childhood-onset asthma had persistent airflow obstruction, irrespective of smoking history. It should be noted that 11.5 pack-years is relatively low exposure to connect cigarette smoking and childhood asthma, but more symptoms may develop as the cohort progresses into later life with more smoke exposure. The strength of the study lies in its complete characterization and long-term follow-up with the patients. The finding should not deter smoking cessation efforts.

C.D.

Hancox RJ, Gray AR, Poulton R, Sears MR: The effect of cigarette smoking on lung function in young adults with asthma.
Am J Respir Crit Care Med. 2016;194:276-284.

Keywords: asthma (child), COPD, risk factors, smoking

Your Mother Should Read This Article Before You Are Born

Intrauterine exposure to maternal smoking is a known risk factor for childhood asthma. However, the effects of the mother's passive exposure to tobacco smoke during pregnancy are unclear. Maternal passive smoking and other types of exposure to smoking were analyzed as risk factors for wheezing during the first 2 years of life.

The researchers performed a meta-analysis of data on nearly 28,000 mother-child pairs from 15 European birth cohorts. The study assessed the independent and combined effects of prenatal exposure to the mothers' active and passive smoking and postnatal exposure to passive smok- • • •

ing on the children's risk of wheezing up to age 2, with adjustment for potential confounders.

Compared to children with no exposure to tobacco smoke, those exposed to maternal passive smoking during pregnancy were significantly more likely to develop wheezing by age 2 years: odds ratio (OR) 1.11. Risk was higher when postnatal passive smoke exposure was added to prenatal passive smoke exposure: OR 1.29. For children with both types of passive smoke exposure plus maternal active smoking during pregnancy, the OR increased to 1.73. The risks were further increased with a family history of allergy.

Mothers' passive exposure to tobacco smoke during pregnancy is a risk factor for childhood wheezing up to age 2. Pregnant women should be advised to avoid passive smoking exposure as well as active smoking. The results support policy recommendations to prevent passive smoke exposure and to offer smoking cessation services for pregnant women and their partners.

COMMENT: Intrauterine exposure to active and passive smoking by the mother is a significant risk factor for childhood wheezing. These data can also be extrapolated to developing countries, where exposure to biomass fuels for cooking and enclosed indoor environments lead to similar adverse outcomes. Increased education initiatives are needed to deal with this preventable cause of morbidity in children.

B.E.C.

Vardavas CI, Hohmann C, Patelarou, et al: The independent role of prenatal and postnatal exposure to active and passive smoking on the development of early wheeze in children.

Eur Respir J. 2016;48:115-124.

Keywords: asthma (child), prevention, smoking, wheezing

nosinusitis/nasal polyps and a long duration of disease.

Cluster 3 (23.0%) included patients with allergic asthma, with or without inhaled corticosteroid treatment. This group, with high rates of allergic rhinitis and allergy to furred pets, had a better prognosis than the other clusters. Cluster 4 (19.4%) consisted of older men with accompanying chronic obstructive pulmonary disease (COPD). Cluster 5 (22.0%) included patients with very mild baseline symptoms; most had previously been considered to have intermittent asthma. About 40% of cluster 5 patients had previous hospitalizations for asthma.

The results identify five clusters of patients with severe or life-threatening asthma exacerbations, along with several important risk factors. Further studies are needed to assess the possibility of phenotype-specific interventions to prevent recurrent severe exacerbations.

COMMENT: In recent years, cluster analyses have been performed on various groups of patients with asthma, particularly severe asthma. This prospective study from Japan studied patients admitted with hypoxia and identified five separate clusters. Some of these have been identified before: allergic, concomitant rhinosinusitis, COPD overlap. One new cluster identified were patients with minimal symptoms during the prior 3 months, with 94% having no symptoms at all! This is good reminder that even patients with very mild asthma can be at risk for severe exacerbations.

D.A.K.

Sekiya K, Nakatani E, Fukutomi Y, et al: Severe or life-threatening asthma exacerbation: patient heterogeneity identified by cluster analysis.

Clin Exp Allergy. 2016;46:1043-1055.

Keywords: asthma (adult), asthma (severe), exacerbations, phenotypes

Phenotypes of Severe Asthma Exacerbations: What's New?

Studies using cluster analysis have found variability in the characteristics of patients with severe or life-threatening asthma exacerbations. This study examined heterogeneity among Japanese patients with severe or life-threatening asthma exacerbations.

The prospective study included 175 patients with severe or life-threatening asthma with hypoxia—defined as a pulse oxygen saturation of less than 90%—admitted to 17 Japanese institutions. Cluster analysis was performed using data from patient and physician questionnaires.

Risk factors for severe exacerbations were current smoking, history of hospitalization for asthma, lower frequency of inhaled corticosteroid use, and high frequency or short-acting beta-agonist use. Cluster analysis identified five distinct groups. Cluster 1 (15.4%) were patients with younger-onset asthma with severe baseline symptoms and a high rate of asthma hospitalizations. Cluster 2 (20.0%) consisted mainly of older women, with a high rate of chronic hyperplastic rhi-

Has Proper Inhaler Use Increased?

Since the first metered-dose inhalers (MDIs) were introduced in the 1960s, studies have reported problems with inhaler technique. Forty years of research were analyzed to assess trends in the most common errors for specific types of inhalers.

A review of the literature from 1975 to 2014 identified 144 articles evaluating errors in inhaler technique for MDIs or dry powder inhalers (DPIs). The studies, including a total of 54,354 participants, all used direct observations of inhaler technique by trained personnel.

For MDIs, the most frequent types of errors were errors of coordination (45%), errors of inhalation speed or depth (44%), and failure of breath-holding after inhalation (46%). For DPIs, failure to fully exhale before inhaling was the most frequent error (46%), followed by failure of breath-holding after inhalation (37%), and incorrect preparation (29%). The overall prevalence of correct technique was 31%, acceptable technique 41%, and poor technique 31%. Rates and types of errors were similar for the two 20-year intervals studied.

The results show consistently high rates of incorrect inhaler technique for both MDIs and DPIs. New approaches to patient education and inhaled drug delivery are urgently needed.

COMMENT: It is well-known that patients frequently use their inhalers incorrectly. However, with the development of newer devices such as DPIs and breath-actuated devices, have inhaler techniques improved? This systematic review analyzed 144 studies regarding inhaler technique. The review found that incorrect use of inhalers is still unacceptably high for all devices, and that the situation does not seem to have improved over the past 40 years! This is a reminder that evaluation and documentation of proper inhaler use (regardless of device) should be part of every asthma patient's history and examination.

D.A.K.

Sanchis J, Gich I, Pedersen S, et al: Systematic review of errors in inhaler use: has patient technique improved over time?
Chest. 2016;150:394-406.

Keywords: asthma (adult), asthma (child), inhaler technique

Are Fungal Sensitizations Correlated with Poor Asthma Control?

Fungi are clinically important predisposing allergens for asthma. Previous studies have suggested that fungal sensitization is associated with asthma exacerbations and emergency department visits. This study from Japan evaluated the association between fungal sensitization and asthma control.

The cross-sectional study included 160 adult asthma patients seen at a Japanese university asthma clinic. Specific IgE measurements found that fungal sensitization was common, especially in men. On logistic regression, fungal sensitization was associated with a fivefold increase in the risk of poor asthma control: odds ratio 5.07. There was no such association for house dust mite, Japanese cedar, pollens, furred animals, or insects.

The strongest association with poor asthma control was for *Penicillum chrysogenum,* OR 8.21; followed by *Aspergillus fumigatus,* OR 6.77. Sensitization to *Penicillum* was associated with male sex, pet ownership, and higher total IgE. However, *Penicillum* sensitization was unrelated to lung function measures or exhaled nitric oxide level. *Penicillum* sensitization was significantly associated with sensitization to *Aspergillus, Cladosporium,* and *Trichophyton.*

In this Japanese population of adult asthma patients, fungal sensitization is correlated with poor asthma control, especially in men. The association appears particularly strong for *Penicillum* and *Aspergillus* sensitization.

COMMENT: Fungal sensitization has been correlated with poorly controlled, severe, labile asthma. In this study sensitization to either *Aspergillus* or *Penicillium* was more strongly associated with poor asthma control than sensitization to dust mite or ragweed. Although limited by their exclusive reliance on in vitro specific IgE measurement, the results suggest that these fungal species may be more important in Japan than *Alternaria* species. Follow-up studies are necessary to clarify whether the presence of certain fungal sensitizations may serve as useful biomarkers of poorly controlled asthma.

C.C.R.

Tanaka A, Fujiwara A, Uchida Y, et al: Evaluation of the association between sensitization to common inhalant fungi and poor asthma control.
Ann Allergy Asthma Immunol. 2016;117:163-168.

Keywords: asthma (adult), fungi, risk factors

Are GERD and Atopy Risk factors for CRS?

Previous reports have suggested an association between gastroesophageal reflux disease (GERD) and chronic rhinosinusitis (CRS), although the nature of the pathophysiologic links remain unclear. A cohort and case-control study was performed to clarify the association between these two conditions.

In a retrospective cohort study including 1,066 patients with CRS, 10.5% also had a history of GERD. These patients were older, more likely to be female, and had a higher body mass index. The patients with CRS plus GERD were more likely to have allergy, odds ratio (OR) 2.89; and allergic rhinitis, OR 2.02. The GERD group also had a longer duration of CRS.

A prospective case-control study included 90 patients with CRS and a group of 81 controls without CRS. Among the CRS cases, GERD was significantly associated with asthma: OR 4.77. The patients with CRS and GERD developed CRS at a younger age and had a longer duration of CRS. In the non-CRS controls, GERD was unrelated to asthma or allergic rhinitis.

Patients with concomitant CRS and GERD have an increased prevalence of atopic disease and asthma, compared to CRS patients without GERD. The combination of GERD and atopy may be a risk factor for the occurrence of CRS. Further research is needed to clarify the mechanisms and clinical implications of these findings.

COMMENT: It has been suggested that GERD is a coexisting factor with the atopic condition in the pathogenesis of CRS. This study found that atopy and asthma were more common in subjects with both GERD and CRS than in those with CRS alone. The authors postulate that coexisting GERD and atopy are potential markers for development of CRS. The study is limited by its reliance on a clinical diagnosis of GERD and the fact that it took place in a tertiary care setting. The take-home message is that GERD and atopy may be coexisting factors in the pathogenesis of CRS.

C.C.R.

Mahdavinia M, Bishehsari F, Hayat W, et al: Prevalence of allergic

rhinitis and asthma in patients with chronic rhinosinusitis and gastroesophageal reflux disease.
Ann Allergy Asthma Immunol. 2016;117:758-762.

Keywords: atopy, CRS, GERD

Be Careful Where You Take a Deep Breath

Patients with asthma-COPD overlap syndrome (ACOS) have faster declines in lung function, more exacerbations, and worse quality of life than those with either diagnosis alone. This study evaluated the impact of air pollution—a known risk factor for asthma and COPD—in patients with ACOS.

The study included adults who resided in Ontario in 1996 who developed asthma between 1996 and 2009 and who were enrolled in the Canadian Community Health Survey. The development of ACOS was assessed during follow-up to 2014. Exposure to fine particulate matter ($PM_{2.5}$) and ozone was assessed using pollution monitoring data.

Incident ACOS occurred in 630 of 6,040 participants with asthma. Compared to participants with asthma alone, the ACOS group had later asthma onset, more frequent emergency department visits, and higher mortality: 27.6% versus 6.7%.

For both pollutants studied, cumulative exposure was significantly associated with ACOS. Adjusted hazard ratios were 2.78 per 10 $\mu g/m^3$ exposure to $PM_{2.5}$ and 1.31 per 10 ppb exposure to ozone.

Among patients with asthma, higher exposure to air pollution is associated with a substantial increase in the risk of developing ACOS. Future studies should assess the interaction between air pollution and other risks in the progression from asthma to COPD.

COMMENT: The association between air pollution and the progression of asthma to COPD continues to strengthen. As shown by studies previously reviewed in *AllergyWatch,* decreased exposure to ambient air pollution exposure has a significant benefit in terms of asthma control. These data are similar to risks of smoking and development of COPD, and make an extremely important public health statement.

B.E.C.

To T, Zhu J, Larsen K, et al: Progression from asthma to chronic obstructive pulmonary disease: is air pollution a risk factor? Am J Respir Crit Care Med. 2016;194:429-438.

Keywords: asthma-COPD overlap syndrome, air pollution

Peripheral Eosinophilia: Useful in COPD Too?

In patients with stable chronic obstructive pulmonary disease (COPD), sputum eosinophilia is an indicator of corticosteroid responsiveness, leading to increased lung function and decreased symptoms. In moderate COPD exacerbations, the subgroup with eosinophilic inflammation have a better response to prednisolone. This study compared outcomes for patients with severe COPD exacerbations with an eosinophilic versus noneosinophilic phenotype.

The study included data on 243 patients hospitalized for severe COPD, participating in a randomized trial of an inpatient intervention. About one-fourth of patients were classified as having eosinophilic exacerbations, based on a peripheral blood eosinophil count of 200 cells/μL or 2% of total neutrophil count or greater. Eosinophilic exacerbations were associated with a lower C-reactive protein value and a lower rate of consolidation on chest radiographs.

After treatment with oral corticosteroids, mean length of stay was nonsignificantly shorter for patients with the eosinophilic phenotype: mean 5.0 days, compared to 6.5 days in those with noneosinophilic exacerbations. The difference was independent of preadmission treatment. Mortality and readmission risk were similar between groups.

For patients with severe COPD exacerbations, the eosinophilic phenotype is associated with a shorter length of hospital stay. The difference in C-reactive protein suggests an opportunity for improved treatment stratification. Because of limited statistical power, further studies are needed.

COMMENT: Peripheral eosinophilia has been associated with corticosteroid responsiveness in stable COPD patients. These investigators performed a post hoc analysis on a study of COPD patients who were admitted with exacerbations. Eosinophilic COPD, defined as a peripheral count of 200 or greater, was found in 25% of patients. Those with eosinophilic exacerbations had a shorter length of stay and less often had concomitant pneumonia. Prospective studies would be helpful to determine if stratification of corticosteroid use in COPD patients would improve health outcomes.

D.A.K.

Bafadhel M, Greening NJ, Harvey-Dunstan TC, et al: Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD.
Chest. 2016;150:320-328.

Keywords: COPD, exacerbations, phenotypes

REVIEWS OF NOTE

COMMENT: This comprehensive review traces the origins of COPD to environmental and developmental factors (other than tobacco smoke), such as prematurity and early childhood illnesses. It emphasizes the need to focus on prevention options (for example, vaccines).

C.D.

Martinez FD: Early-life origins of chronic obstructive pulmonary disease.
N Engl J Med. 2016; 375:871-878.