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

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FEATURE ARTICLES

Goodbye ICS/LABA Black Box!

In 2010 the FDA mandated a "black box" warning for all long-acting β_2-agonists (LABAs) marketed for treatment of asthma. Subsequent analyses have reached mixed conclusions regarding the safety of LABAs for asthma. In this paper, a joint oversight committee presents a combined analysis of four FDA-mandated manufacturer trials comparing the safety of inhaled corticosteroid (ICS)/LABA therapy versus ICS alone, focusing on relatively rare but serious adverse events.

The intention-to-treat analysis included 36,010 adolescents and adults with persistent asthma, enrolled in four 26-week, multicenter trials. Patients were randomly assigned to double-blind treatment with an ICS/LABA combination or ICS alone. The primary outcome was a composite of asthma-related intubation or death. Post hoc secondary analyses included a composite of serious asthma-related events (hospitalization, intubation, or death) as well as asthma exacerbations.

Serious adverse events occurred in 4 patients: three asthma-related intubations (two with ICS alone and one with ICS/LABA) and two deaths (both with ICS/LABA). On secondary analysis, rates of serious asthma-related events were almost identical between groups: 0.60% with ICS alone and 0.66% with ICS/LABA.

Combination therapy was associated with a reduction in exacerbations: 11.7% versus 9.8%, relative risk 0.83. The reduction in exacerbations with ICS/LABA appeared to be less in subgroups defined by adolescent age group, black or Asian race/ethnicity, and class II or III obesity. Smoking and older age did not affect this outcome.

Analysis of four FDA-mandated trials shows no increase in serious asthma-related events with an ICS/LABA combination compared to ICS alone. Combination therapy is associated with a lower risk of exacerbations. The findings sup- • • •

FEATURE ARTICLES

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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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port current guidelines regarding the use of ICS/LABA combinations, as well as the recent FDA decision to remove the black box warning.

COMMENT: The saga of the black box warning on medications containing LABAs has been a bit of a rollercoaster ride. This article by an independent joint oversight committee analyzed data from recent published and unpublished studies on the risk of severe events in patients taking various ICS/LABA combinations. The data were reassuring. In contrast to the infamous SMART study, ICS/LABA therapy did not result in a higher risk of serious asthma-related events but did reduce asthma exacerbations. The findings led the FDA to remove the black box warning from ICS/LABA in December 2017. Hooray!

D.A.K.

Busse WW, Bateman ED, Caplan AL, et al: Combined analysis of asthma safety trials of long-acting β_2-agonists. N Engl J Med. 2018;378:2497-2505.

Keywords: asthma (adult), black box, LABAs

Dupilumab Can Treat Uncontrolled Asthma

In patients with severe asthma, biologic agents have the potential to control symptoms and exacerbations and improve lung function, while reducing the need for systemic glucocorticoids. Dupilumab, a fully human Ig4 monoclonal antibody against the interleukin-4 receptor subunit α (IL-4Rα) of the IL-4 and IL-13 receptors, can reduce type 2 inflammation. The phase 3 LIBERTY ASTHMA VENTURE trial evaluated dupilumab for safety and efficacy in patients with glucocorticoid-dependent severe asthma.

Two hundred ten patients receiving oral glucocorticoids for severe asthma were randomly assigned to add-on therapy with dupilumab, 300 mg, or placebo every 2 weeks for 24 weeks. Patients underwent downward adjustment of glucocorticoid dose for 20 weeks, followed by 4 weeks on a maintenance dose. Reduction in glucocorticoid dose was assessed, along with exacerbation rates and lung function.

Glucocorticoid dose decreased by about 70% with dupilumab, compared to a 42% reduction in the placebo group. Dose was reduced by at least half in 80% of the dupilumab group versus 50% of the placebo group; complete discontinuation was achieved in 48% and 25% of patients, respectively. Even with the lower oral glucocorticoid dose, dupilumab was associated with a 59% reduction in severe exacerbations and a 0.22 L increase in FEV_1, compared to placebo. The dupilumab group had higher rates of injection-site reactions (9% versus 4%) and transient blood eosinophilia (14% versus 1%).

Add-on dupilumab therapy in patients with severe asthma can reduce oral glucocorticoid dose, reducing the severe exacerbation rate, and improve lung function. A reduction in exhaled nitric oxide suggests that dupilumab has a broader effect on type 2 inflammation, compared to agents targeting eosinophils alone.

About one-fifth of asthma patients have uncontrolled, moderate to severe symptoms despite recommended controller therapy. By inhibiting IL-4 and IL-13, dupilumab can block type 2 inflammation in allergic diseases. The LIBERTY ASTHMA QUEST trial evaluated the safety and efficacy of dupilumab in patients with uncontrolled asthma.

The phase 3 trial included 1,902 adolescents and adults with uncontrolled, moderate-to-severe asthma. Patients were randomly assigned to add-on therapy with dupilumab, given in a subcutaneous dose of 200 mg (631 patients) or 300 mg (633 patients) every 2 weeks; or matched-volume placebo (317 and 321 patients, respectively). Treatment continued for 52 weeks. The main outcomes of interest were asthma exacerbation rate and change in prebronchodilator FEV_1 from baseline to 12 weeks.

Annualized severe exacerbation rate was 0.46 with the 200 mg dose of dupilumab versus 0.87 with the corresponding placebo: a 47.7% reduction. Dupilumab 200 mg was also associated with a 0.32 L increase in FEV_1, with a difference of 0.14 L compared to placebo. Among patients with a high initial blood eosinophil count of 300/mm^3 or greater, the annualized severe exacerbation rate was 0.37 with the lower dose of dupilumab versus 1.08 with placebo: a 65.8% reduction.

All of these outcomes were similar for patients assigned to dupilumab 300 mg, compared to placebo. Blood eosinophilia occurred in 4.1% of patients receiving dupilumab versus 0.6% of the placebo groups.

Dupilumab reduces exacerbation rate while improving lung function in patients with moderate-to-severe, uncontrolled asthma. The results also show improved asthma control and symptom relief with add-on dupilumab. The benefit of this biologic therapy is greater among patients with higher baseline eosinophil levels.

COMMENT: Two new studies herald the strong possibility of yet another biologic option for treatment of uncontrolled asthma: namely, dupilumab. In LIBERTY ASTHMA VENTURE, dupilumab reduced the use of oral glucocorticoids in 210 patients with severe asthma. The concomitant reduction in severe exacerbations and improvement in FEV_1 were also observed in LIBERTY ASTHMA QUEST, a phase 3 trial including 1,902 patients with uncontrolled asthma. In both studies, there was transient eosinophilia but no increase in conjunctivitis (in contrast to atopic dermatitis studies). Notably, treatment effects were greater in patients with higher baseline blood eosinophil levels and higher exhaled nitric oxide, suggesting that dupilumab inhibits type 2 inflammation more broadly than targeting eosinophils alone.

With the exciting recent spike in the emergence of biologics to treat uncontrolled asthma, it becomes critically important to differentiate between these options, and to be able to provide personalized care. Head-to-head trials focusing on delineation of responders and non-responders, identification of novel predictive biomarkers, and on "curing" asthma are imperative. Also see the accompanying editorial by Drazen and Harrington (N Engl J Med. 2018; 378:2533-2534).

C.D.

Rabe KF, Nair P, Brusselle G, et al: Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378:2475-2485.

Castro M, Corren J, Pavord ID, et al: Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018;378:2486-2496.

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

As-Needed Inhaled Budesonide-Formoterol: An Option in Mild Asthma

Patients with mild asthma often have poor adherence to maintenance therapy with inhaled corticosteroids, instead relying on short-acting β_2-agonists for symptom relief. This trial evaluated a combination of budesonide-formoterol, used as-needed, as an alternative approach to management of mild asthma.

The Symbicort Given as Needed in Mild Asthma (SYGMA 1) trial included 3,849 patients with mild asthma, aged 12 years or older. Patients were randomly assigned to 52 weeks of treatment with twice-daily placebo plus as-needed terbutaline, 0.5 mg; twice-daily placebo plus as-needed budesonide/formoterol, 200 μg/6 μg; or twice-daily budesonide plus as-needed terbutaline. Asthma symptom control was compared between groups along with secondary outcomes.

On analysis of 3,836 patients, mean percentage of weeks with well-controlled asthma per patient was 34.4% with as-needed budesonide-formoterol, 31.1% with as-needed terbutaline, and 44.4% with budesonide maintenance therapy. As-needed budesonide-formoterol was superior to as-needed terbutaline, odds ratio 1.14; but inferior to maintenance budesonide, odds ratio 0.64. Annual severe exacerbation rate was 0.20 with terbutaline, 0.07 with budesonide–formoterol, and 0.09 with budesonide maintenance therapy. Budesonide-formoterol was superior to terbutaline, rate ratio 0.36, but not significantly different from budesonide maintenance therapy.

Adherence rate to budesonide maintenance therapy was 78.9%. Patients assigned to as-needed budesonide-formoterol had a median daily inhaled glucocorticoid dose of 57 μg, compared to 340 μg in the budesonide maintenance group. Asthma control score and lung function were better with as-needed budesonide versus as-needed terbutaline, but not as good as with maintenance budesonide.

As-needed budesonide-formoterol is more effective than as-needed terbutaline for patients with mild asthma. The budesonide-formoterol combination is similar to budesonide maintenance therapy in reducing exacerbation risk, at a much lower inhaled corticosteroid dose and without the need for a twice-daily inhaler regimen.

The SYGMA 1 trial found that, in patients with mild asthma, as-needed budesonide-formoterol could reduce severe exacerbations to a rate similar to that of budesonide maintenance therapy. The SYGMA 2 trial used a more pragmatic design to compare these two strategies.

The study included 4,215 adolescents and adults with mild asthma. Patients were randomly assigned to as-needed budesonide-formoterol or twice-daily maintenance budesonide therapy plus as-needed terbutaline. Patients did not receive reminders regarding daily inhaler use. The • • •

main outcome of interest was annualized rate of severe exacerbations, with a prespecified noninferiority limit of 1.20.

Outcome analysis included 4,176 patients. Annualized severe exacerbation rate was 0.11 with as-needed budesonide-formoterol and 0.12 with budesonide maintenance therapy. Median daily inhaled glucocorticoid dose was 66 μg with as-needed budesonide-formoterol versus 267 μg with maintenance budesonide. The maintenance group had a small but significant improvement in asthma control score. Adverse events were similar between groups.

As-needed budesonide-formoterol is noninferior to budesonide maintenance therapy in reducing severe exacerbation risk in patients with mild asthma. While asthma symptom control is not as good as with twice-daily maintenance therapy, the as-needed combination greatly reduces total inhaled glucocorticoid dose. The authors note that the adherence rates in the SYGMA trials are "substantially higher" than in real-world studies of asthma maintenance therapy.

COMMENT: The option to use an asthma inhaler on-demand would be eagerly welcomed by many of our patients with asthma, particularly those concerned about the cumulative effects of regular inhaled steroid use. The radical concept of using an as needed anti-inflammatory agent along with a SABA in patients with mild asthma has shown promise in earlier trials. The two SYGMA trials take this concept a step further, taking advantage of the rapid onset of action of the long-acting β_2-agonist formoterol. In both studies, on-demand use of the budesonide-formoterol combination was similar to regular budesonide maintenance in reducing asthma exacerbations. Furthermore, this objective was achieved with less than a quarter of the amount of ICS used by the regular maintenance group!

On the flip side, symptom control and other composite measures were better attained in the maintenance group. If we factor in potentially improved patient adherence and decreased pharmacy costs, the on-demand strategy may be a compromise choice that many eligible patients will opt for. As we well know, many of them have already adopted this strategy! The good news is that we can now support their choice based on evidence. Also see the editorial by Lazarus (N Engl J Med. 2018;378:1940-1942).

C.D.

O'Byrne PM, FitzGerald M, Bateman ED, et al: Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med. 2018;378:1865-1876.

Bateman ED, Reddel HK, O'Byrne PM, et al: As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med. 2018;378:1877-1887.

Keywords: as-needed therapy, asthma (mild), ICS/LABA

Does Response to Omalizumab in Severe Asthma Depend on Blood Eosinophils?

The anti-IgE monoclonal antibody omalizumab is indicated as add-on therapy for children and adults with severe allergic asthma (SAA). This study evaluated the baseline blood eosinophil level as a predictor of response to omalizumab in SAA.

The retrospective analysis included 872 patients with SAA – 723 adults and 149 pediatric patients aged 6 to 17 – treated with omalizumab in France between December 2015 and September 2016. Response to omalizumab was assessed by the physician's overall evaluation, based on the five-point Global Evaluation Treatment Effectiveness scale; a 40% or greater reduction in annualized exacerbation rate; and a combination of these two criteria. Response rates were analyzed in terms of the patients' blood eosinophil count in the year before starting omalizumab.

Initial blood eosinophil count was 300 cells/μL or higher in 52.1% of adults and 73.8% of pediatric patients. Based on physician's evaluation, 67.2% of adults and 77.2% of children responded to omalizumab. Based on a 40% or greater reduction in exacerbation rate, responses were achieved in 71.1% of adults and 75.8% of children. Analysis using the combined criteria suggested a similar response rate above and below the 300 cells/μL blood eosinophil cutoff: 58.4% and 58.1%, respectively. Response tended to be better in nonsmokers compared to current or former smokers.

The retrospective study suggests a high response rate to omalizumab therapy in adults and children with SAA. Effectiveness appears similar in patients with high or low baseline blood eosinophil levels. The authors call for further studies of biologic therapies "targeting overlapping populations of patients with severe persistent allergic asthma and a high blood eosinophil count."

COMMENT: This study from France gives us reassuring information from SAA patients, both minors and adults. Blood eosinophil counts over a wide range of patients who meet the inclusion criteria for omalizumab may lead to similar outcomes. Approximately 30% of the cohort were current or former smokers. Although the study did not compare the effectiveness of omalizumab with anti-IL-5 biologics or dupilumab, the findings reassure us that eosinophil count is not a major predictor of response to omalizumab. This suggests that the use of omalizumab in "Th2-low" patients may achieve a response. As more data accumulate, we will better understand which biologic to choose for patients who do not respond to GINA step 4 and 5 therapy. See also the editorial by Busse (Eur Respir J. 2018;51:1800730).

B.E.C.

Humbert M, Taillé C, Mala L, et al: Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J. 2018;51:1702523.

Keywords: asthma (allergic), asthma (severe), biologics; omalizumab

Are Daycare Centers an Allergy Nightmare?

Indoor allergen sensitization in early childhood is associated with an increased risk of developing asthma later in life. Relatively little is known about children's exposure to allergens outside the home. This German study compared allergen levels in daycare centers and home settings.

Using electrostatic dust collectors, the researchers collected settled airborne dust samples four times a year from 20 daycare centers, for a total of 620 samples. The analysis also included 602 samples from the homes of children and daycare workers. Exposure to indoor allergens in daycare centers versus homes were analyzed, along with threshold levels to differentiate homes with a cat or dog versus homes without pets.

On average, daycare centers had higher allergen levels than the children's or workers' homes. Of the daycare samples, 96% were positive for dust mite (DM) allergen, 95% for Can f 1, 90% for Fel d 1, and 83% for Mus m 1. Of home samples, 84% were positive for DM, 48.5% for Can f 1, 33% for Fel d 1, and 43% for Mus m 1.

Threshold levels for identifying homes with pets were 75 mg/m^2 for Can f 1 and 46 ng/ m^2 for Fel d 1. These thresholds were exceeded for Can f 1 in 37% of daycare samples and for Fel d 1 in 54%. Factors influencing allergen levels included the type of room, the frequency of room use, and the season; carpeted floors were not a significant factor.

Daycare centers may have higher indoor allergen levels than home settings. In many daycare samples, levels of dog and cat allergens are similar to those of homes with pets. The study identifies allergen levels highly predictive of the presence or a dog or cat at home.

COMMENT: Previous studies have demonstrated that early sensitization to indoor allergens is a risk factor for the development of asthma, yet little is known about allergen levels in daycare settings. Sander and colleagues found that mite, mouse, as well as cat and dog allergen levels were higher in daycare centers compared to homes. Pet allergen levels in the daycare setting often reached levels of households with pets. This certainly makes you think twice about the potential impact of daycare and allergy – if not for the children, then certainly for the employees.

J.J.O.

Sander I, Lotz A, Neumann HD, et al: Indoor allergen levels in settled airborne dust are higher in day-care centers than at home.
Allergy. 2018;73:1263-1275.

Keywords: allergen levels, daycare, pet allergens

Indoor Allergen Avoidance May Not Improve Asthma

Measures to reduce exposure to indoor allergens have long been a part of asthma clinical practice guidelines. As part of a new update of the National Asthma Education and Prevention Program guidelines, the evidence on the effectiveness of indoor allergen reduction interventions was reviewed.

The systematic review was performed by the Agency for Healthcare Research and Quality via its Evidence-Based Practice Centers. A comprehensive search identified 59 randomized and eight nonrandomized trials of eight interventions to reduce indoor allergens: acaricide, air purification, carpet removal, high-efficiency particulate air filtration (HEPA) vacuums, mattress covers, mold removal, pest control, and pet removal. Thirty studies evaluated multicomponent interventions.

Due to heterogeneity of the studies, meta-analysis was not possible. Few studies used standardized measures of asthma outcomes. For most interventions, the data were inconclusive or showed no significant effect on outcomes. None of the allergen-reduction interventions had high-strength evidence of improvement in validated measures of asthma control, exacerbations, healthcare use and costs, pulmonary physiology, or asthma-related quality of life.

Multicomponent interventions including HEPA vacuums or pest control produced moderate strength of evidence for reduced exacerbations. For improvement in quality of life, there was low quality of evidence in support of air purifiers, moderate evidence in multicomponent studies including HEPA vacuums, and low evidence in multicomponent studies including pest control.

The review finds only weak evidence for the effectiveness of indoor allergen reduction in asthma management. Some multicomponent interventions improve some asthma outcomes, but no specific combination of interventions is more effective. Future studies of these interventions should include validated asthma outcome measures with adequate sample sizes to show meaningful differences.

COMMENT: Current guidelines recommend reducing exposure and controlling environmental allergens for patients with allergic asthma. The NHLBI working group and AHRQ report this systematic review, which used more rigorous criteria than prior reports. The strength of evidence was inconclusive to support true efficacy of the interventions to reduce indoor allergens on asthma outcomes. Although some multicomponent interventions like HEPA vacuum or pest control may improve some aspects of asthma outcomes, the question of how best to counsel our patients without sound evidenced-based data still presents a quandary.

S.M.F.

Leas BF, D'Anci KE, Apter AJ, et al: Effectiveness of indoor allergen reduction in asthma management: a systematic review.
J Allergy Clin Immunol. 2018;141:1854-1869.

Keywords: allergen reduction, asthma (adult), asthma (child)

Children with High-Risk Genetic Variant Benefit More from Early Cat Exposure

Early-life exposure to pets has been thought to increase the risk of childhood asthma, but previous studies of this issue have reported conflicting results. Gene-environment interactions might explain the varying findings. This study evaluated potential interactions between pet exposure and 17q21 high-risk variant for childhood asthma.

Genotyping for the single nucleotide polymorphism rs7216389 in the chromosome 17q21 locus – the strongest known genetic risk factor for early childhood asthma – was performed in 377 children from the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$). Children were followed up to age 12 for the development of asthma; episodes of pneumonia and bronchiolitis up to age 3 were evaluated as well. The possible interaction between 17q21 risk genotype and early-life dog and cat ownership was analyzed.

For children with the high-risk TT genotype, early exposure to cat and/or dog was associated with a lower prevalence of asthma: adjusted hazard ratio (HR) 0.16. In contrast, there was no significant relationship between pet exposure and asthma risk for children with the CC/CT genotype. The protective effect of pet exposure among children with the TT genotype was limited to those with higher exposure to cat allergen, HR 0.83. There was no significant interaction between genotype and dog allergen exposure.

The TT genotype was also associated with increased risk of pneumonia and bronchiolitis in early childhood, and this association was weaker in children exposed to cat: adjusted incidence rate ratio 0.47. The interaction between cat exposure and risk genotype was similar in a replication analysis of an unselected COPSAC$_{2010}$ cohort with follow-up to age 5.

In children with the high-risk TT genotype, early-life exposure to cat attenuates the increased genetic susceptibility to childhood asthma, pneumonia, and bronchiolitis. Dog exposure does not affect risk in children with the TT genotype, and neither type of pet exposure affects risk in children with the CC/CT genotype. This gene-environment interaction may help to explain the conflicting findings regarding the effects of early-life pet exposure on childhood asthma risk.

COMMENT: These Danish researchers report findings from the unique COPSAC birth cohort of children at high risk for asthma. The study analyzed animal exposure at home in early childhood and a genetic variant in chromosome 17q21 that is known to be associated with childhood asthma. The data showed that children with a high-risk genotype who had been exposed to cat had a reduced risk of developing asthma. This effect wasn't found with dog exposure. Although the study doesn't directly solve the "nature versus nurture" debate, it does reaffirm that they are intertwined.

S.M.F.

Stockholm J, Chawes BL, Vissing N, et al: Cat exposure in early life decreases asthma risk from the 17q21 high-risk variant. J Allergy Clin Immunol. 2018;141:1598-1606.

Keywords: asthma (child), cat allergen, dog allergen, hygiene hypothesis

Anticholinergic Agents and Dementia Risk

Anticholinergic drugs, which block the neurotransmitter acetylcholine, are used for a wide range of indications, including allergic diseases. Previous studies have suggested that prolonged exposure to anticholinergic drugs might be associated with cognitive decline or dementia. The association between anticholinergic medications and dementia risk was assessed using a large primary care database.

The case-control study included 40,770 older adults with dementia, identified from the UK Clinical Practice Research Datalink. Cases were matched to 283,933 controls without dementia. Exposure was assessed using the Anticholinergic Cognitive Burden (ACB) scale, considering exposure to different categories of anticholinergic drugs over 4 to 20 years before dementia diagnosis. Associations with incident dementia were assessed, with adjustment for potential confounders.

At least one drug with an ACB score of 3 – indicating "definite anticholinergic activity" – was prescribed to 35% of dementia cases and 30% of controls. Any anticholinergic drug in this category was associated with an increased risk of dementia: adjusted odds ratio 1.11. Dementia risk also increased with higher average ACB score.

By indication, dementia risk increased with greater exposure to antidepressant, urologic, and antiparkinsonian drugs with an ACB score of 3, although not with exposure to gastrointestinal drugs. The associations remained significant for exposure 15 to 20 years before dementia diagnosis. Analysis restricted to new users showed little change in the strength of the associations, particularly for antidepressant and urologic drugs with an ACB of 3.

Exposure to some classes of anticholinergic medications is strongly associated with future risk of developing dementia. Other anticholinergics do not appear to be related to dementia risk, while the association remains unknown for some of these drugs. The authors suggest that clinicians should consider the long-term cognitive effects of anticholinergic drugs when performing risk-benefit analysis.

COMMENT: This case-control study extends previous findings associating exposure to agents we prescribe – particularly for refractory chronic urticaria – with an increased risk of developing dementia. The study associates this risk with antidepressant medications, and reports a "trend" for risk with antihistamines that penetrate the blood-brain barrier and can cause acute delirium. These findings are clearly relevant for interpretation of recommendations for management of chronic urticaria (J Allergy Clin Immunol.

2014;133:1270-1277). Advancing patients with a refractory course to a trial of doxepin will need to be considered more carefully from the standpoint of balancing potential for benefit with potential for harm.

D.M.L.

Richardson K, Fox C, Maidment I, et al: Anticholinergic drugs and risk of dementia: case-control study. BMJ. 2018;360:k1315.

Keywords: anticholinergic drugs, chronic urticaria, dementia

Morbidity of Penicillin Allergy

Self-reported penicillin allergy leads to patients being prescribed more broad-spectrum antibiotics, potentially leading to infection with drug-resistant bacteria. This population-based study examined the association between penicillin allergy and risk of infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile.*

Using the UK Health Improvement Network database, the researchers identified 64,141 adults with penicillin allergy and 237,258 matched controls. Both groups were free of previous MRSA or *C. difficile* infection. The association between newly documented penicillin allergy and the incidence of these drug-resistant infections was evaluated. Use of beta-lactam and alternative antibiotics was evaluated as well.

Over a mean 6 years of follow-up, MRSA was diagnosed in 1,365 patients and *C. difficile* in 1,688. The incidence of both drug-resistant infections was increased among patients with penicillin allergy: adjusted hazard ratio 1.69 for MRSA and 1.26 for *C. difficile.* Patients with penicillin allergy had increased use of macrolides, clindamycin, and fluoroquinolones: incidence rate ratio 4.15, 3.89, and 2.10, respectively. These alternative antibiotics were associated with increased risks of MRSA and/or *C. difficile.* Use of beta-lactam alternatives mediated 55% of the effect of penicillin allergy on MRSA risk and 35% of the effect on *C. difficile* risk.

Patients with recorded penicillin allergy are at higher risk of incident MRSA and *C. difficile,* and these risks are largely related to the increased use of alternative antibiotics. The researchers conclude, "[S]ystematic efforts to confirm or rule out the presence of true penicillin allergy may be an important public health strategy to reduce the incidence of MRSA and *C. difficile".*

COMMENT: When patients who furnish a history of allergy to penicillin or a penicillin-like drug require antibiotic administration, an alternative antibiotic (eg, quinolone, macrolide, or vancomycin) is commonly prescribed. This important study provides additional evidence that these alternative agents are associated with heightened risk for untoward effects: increased rates of MRSA and *C. difficile.* More frequent allergy/immunology evaluation, including immediate hypersensitivity skin testing to penicillin reagents, can lead to improved outcomes. This is an important opportunity for our specialty to address an imminent public health challenge.

D.M.L.

Blumenthal KG, Zhang Y, Walensky RP, Choi HK: Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. BMJ. 2018;361:k2400.

Keywords: antibiotics, drug allergy, penicillin allergy

Pretreatment for Contrast Procedures: 5-Hour versus 13-Hour Regimen

Patients at risk of allergic-like reactions to contrast media may receive oral corticosteroid pretreatment, most commonly in a 13-hour regimen. Accelerated intravenous corticosteroid regimens may be used in urgent or other situations, despite a lack of supporting evidence. This study compared the rate of allergic-like breakthrough reactions to contrast media in patients receiving a 5-hour IV corticosteroid regimen versus the standard 13-hour oral regimen.

The retrospective analysis included 202 patients who received an accelerated 5-hour IV corticosteroid regimen before receiving low-osmolality, iodine-based contrast media for computed tomography examination. A comparison group included 626 patients receiving the 13-hour oral regimen; all patients had a previous allergic-like or unknown reaction to contrast media. The breakthrough reaction rate was compared between groups.

Breakthrough reactions occurred in 2.5% of patients receiving the 5-hour IV regimen compared to 2.1% with the 13-hour oral regimen. The upper limit of the confidence interval for the difference between groups was 3.7%, which was under the specified noninferiority margin of 4.0%. Of the total of four breakthrough reactions, all were of equal or lesser severity than the initial reaction.

A 5-hour IV corticosteroid premedication regimen is "at least not substantially less effective" than the standard 13-hour oral regimen in patients with prior contrast reactions. The authors suggest that the accelerated IV regimen can be considered for patients with competing medical priorities, including emergency or inpatient examinations.

COMMENT: Allergy/immunology physicians routinely recommend pretreatment with a 13-hour diphenhydramine and prednisone regimen for patients with prior reactions. But this may be associated with harms for inpatients – including higher rates of infection and prolonged length of stay (Radiology 2016;279:492-501) – that may exceed benefit. This study offers evidence that an accelerated 5-hour regimen is noninferior to the standard 13-hour regimen for risk of breakthrough reactions. However, the study was underpowered for moderate and severe reactions. Additional studies • • •

with more clearly defined patient selection will be required before we alter our recommendations for a 13-hour pretreatment regimen for patients with prior anaphylactoid reactions.

D.M.L.

Mervak BM, Cohan RH, Ellis JH, et al: Intravenous corticosteroid premedication administered 5 hours before CT compared with a traditional 13-hour oral regimen. Radiology. 2017;285:425-433.

Keywords: contrast reactions, drug allergy

Evaluating Perioperative Anaphylaxis: Still Plenty of Room for Improvement

Especially in more severe reactions, perioperative anaphylaxis warrants specialist evaluation. This paper presents the findings of a 1-year audit of specialist perioperative allergy clinic services in the United Kingdom.

The Royal College of Anaesthetists 6th National Audit Project (NAP6) included data on 266 incidents of grade 3 to 5 perioperative anaphylaxis occurring at UK hospitals over a 1-year period. Anaphylaxis with a trigger was identified in 192 cases (72%). Of these, 140 reactions (40%) met NAP6 criteria for IgE-mediated allergic anaphylaxis. Another 13% of cases were classified as nonallergic anaphylaxis due to lack of positive IgE tests and 3% as non-IgE-mediated anaphylaxis.

Peak tryptase level exceeded 14 μg/L in 14% of cases. Tryptase levels varied in distribution and median values for grade 3 versus 4 reactions. Chlorhexidine was associated with the slowest reaction speeds, while reactions were fastest for suxamethonium, muscle relaxants, and the antibiotics teicoplanin and amoxicillin/clavulanic acid. Median T1 levels were similar in allergic versus nonallergic anaphylaxis. Some cases of allergic anaphylaxis had tryptase increases that would only be detected by dynamic tryptase calculations.

Comparison with the 2016 NAP6 baseline survey identified several performance issues, including lack of testing for chlorhexidine and latex, lack of harmonized testing practices, and poor coverage of all possible culprit exposures. There was low use of challenge testing and delayed assessment even in some urgent cases. Communication with and data provided to patients was inadequate, particularly in terms of avoidance and communication of test results. Information on skin test methods was inadequate for assessment of technique.

While the audit shows effective evaluation of perioperative anaphylaxis in the United Kingdom, several shortcomings are identified. The authors highlight areas for improvement, including timely access to evaluation and standard clinical reports. Dynamic tryptase evaluation is recommended to improve detection in cases with peak tryptase less than 14 μg/L.

COMMENT: This is a fairly large study from a group of specialized clinics in the UK that evaluate perioperative anaphylaxis. Despite perceived self-adherence to national guidelines for evaluation, actual adherence was low and often patients were not tested to many relevant allergens (especially chlorhexidine). The study also looked at "dynamic" tryptase testing (formula measuring acute versus baseline) and found it helpful in identifying an additional 16% of anaphylaxis cases. Interestingly, tryptase levels also varied by culprit drug, with suxamethonium reactions causing the highest elevations.

D.A.K.

Egner W, Cook TM, Garcez T, et al: Specialist perioperative allergy clinic services in the UK 2018: results from the Royal College of Anaesthetists Sixth National Audit Project (NAP6) investigation of perioperative anaphylaxis. Clin Exp Allergy. 2018;48:846-861.

Keywords: anaphylaxis, drug allergy, perioperative anaphylaxis

Anaphylaxis Severity – New Data on Risk Factors

Information about eliciting and augmenting factors may help to avoid serious episodes of anaphylaxis. This study used the European Anaphylaxis Registry to examine factors associated with severe anaphylaxis.

The analysis included 7,316 cases of anaphylaxis reported by 122 European centers. Females accounted for approximately 52% of patients and children for 29%. Factors associated with a higher risk of severe anaphylaxis were identified by logistic regression analysis.

For each year of age, the odds of severe anaphylaxis increased by 1.6%. The combination of older age and concomitant mastocytosis was associated with a threefold increase in severe anaphylaxis risk: odds ratio (OR) 3.1. Other risk factors included vigorous physical activity, OR 1.5; male sex, OR 1.2; and clinically relevant psychological burden, OR 1.4. Risk was also increased for patients with concomitant use of beta-blockers or angiotensin-converting enzyme inhibitors: OR 1.86 and 1.28, respectively. Anaphylactic reactions elicited by drugs were also more likely to be severe, compared to other elicitors: OR 1.43.

The study identifies a wide range of endogenous and exogenous factors associated with severe anaphylaxis. This information may be helpful in targeting patients at higher risk for more intensive preventive measures.

COMMENT: This interesting study mines the European Anaphylaxis Registry data, attempting to identify factors related to severity of anaphylaxis. The most important risk factors were older age with concomitant mastocytosis, vigorous activity, male sex, "psychologic burden," and use of beta-blockers or ACE inhibitors with temporal allergen exposure. The researchers conclude that it may be possible to identify patients who require intensified preventative measures, as they are at higher risk of severe ana-

phylactic reactions.

J.J.O.

Worm M, Francuzik W, Renaudin J-M, et al: Factors increasing the risk for a severe reaction in
anaphylaxis: an analysis of data from The European Anaphylaxis Registry. Allergy. 2018;73:1322-1330.

Keywords: anaphylaxis, risk factors

ED Treatment of Anaphylaxis to Stinging Insects Is Getting Better

Stinging insect anaphylaxis is a common and serious reason for emergency department (ED) visits. Previous studies have reported limited concordance with guideline recommendations for ED care. This study analyzes trends in ED concordance with guidelines for management of stinging insect anaphylaxis.

The researchers analyzed two multicenter retrospective studies of ED care for patients with stinging insect-related acute allergic reactions. The studies included 182 patients treated in 1999-2001 and 148 treated in 2013-2015; all were treated at the same 14 North American EDs. Trends in concordance with four guideline recommendations were analyzed: epinephrine treatment, discharge prescription of an epinephrine autoinjector, referral to an allergist/immunologist, and instructions to avoid the offending allergen.

Rates of treatment with epinephrine, before or after arrival in the ED, increased from 30% in 1999-2001 to 49% in 2013-2015. Discharge prescriptions for an epinephrine autoinjector also increased, from 34% to 57%. In contrast, the rate of allergy/immunology referral decreased from 28% to 12%; while allergen avoidance instructions were unchanged, 23% versus 24%. The percentage of patients receiving at least three of the four interventions increased nonsignificantly, from 10% to 16%.

The study suggests some improvement in ED management of stinging insect anaphylaxis over the past 15 years, particularly in terms of increased use of epinephrine and increased prescribing of epinephrine autoinjectors. The authors suggest that the decline in allergist/immunologist referrals might reflect ED providers' lack of awareness of the effectiveness of venom immunotherapy.

COMMENTS: While proper identification of anaphylaxis in the ED setting has varied, this comparison of data from two multicenter retrospective studies shows that providers are following the guidelines more now than 15 years ago. The authors question the reason for decreased referrals to allergists. As practicing allergists, we should continue to collaborate with our ED colleagues in order to ensure that patients receive proper follow-up.

V.H.-T.

Clark S, Boggs KM, Balekian DS, et al: Changes in emergency department concordance with guidelines for the management of stinging insect-induced anaphylaxis 1999-2001 vs 2013-2015.
Ann Allergy Asthma Immunol. 2018;120:419-423.

Keywords: anaphylaxis, emergency department, venom allergy

More Potential Options for HAE Prevention

Patients with hereditary angioedema (HAE) have mutations of the C1 esterase inhibitor gene, leading to over-activation of the kallikrein-bradykinin cascade. New approaches to preventive treatment are needed. This proof-of-concept study evaluated a new oral small-molecule plasma kallikrein inhibitor, BCX7353, as a new treatment to prevent HAE attacks.

The three-part study included 77 patients with HAE, enrolled in Europe, Canada, and Australia. All had type I or II HAE with at least two attacks per month. Patients were randomly assigned to 28 days of treatment with placebo or one of four doses of BCX7353: 62.5, 125, 250, or 350 mg once daily. The primary efficacy outcome was the occurrence of confirmed angioedema attacks.

At doses of 125 mg or higher, BCX7353 was associated with a lower rate of confirmed angioedema attacks: a 73.8% reduction compared to placebo. Forty-three percent of patients were attack-free at the 125 mg dose. The 125 and 250 mg doses of BCX7353 were also associated with improved quality of life scores. Abdominal adverse events, mainly grade 1, were most common in the 250 and 350 mg dose groups. Across the dose range studied, BCX7353 produced dose-dependent inhibition of kallikrein.

BCX7353 is a promising once-daily oral kallikrein inhibitor for prevention of HAE attacks. At a 125 mg/d dose, it produces good reduction in angioedema attacks with improvement in quality of life. Longer-term studies are needed.

COMMENT: Options for prevention of HAE are still limited. This study evaluated a different oral kallikrein inhibitor, BCX7353, administered once daily. Similar to previous trials of oral kallikrein inhibitors, gastrointestinal effects were common, especially at higher doses. These effects likely impacted the results, which suggested an optimal dose of 125 mg. Larger trials will be needed to determine safety and efficacy of this medication. A once-daily oral medication with only mild adverse effects would be appealing.

D.A.K.

Aygören–Pürsün E, Bygum A, Grivcheva–Panovska V, et al: Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema.
N Engl J Med. 2018;379:352-362.

Keywords: HAE, kallikrein inhibitors, prevention

Respiratory Symptoms in Young Adults Predict Later Lung Disease

Aside from the effects of cigarette smoking, little is known about the factors associated with accelerated decline in lung function. This study evaluated a wide range of pulmonary symptoms in young adults for association with later decline in lung function and incident chronic obstructive pulmonary disease (COPD).

The analysis included data on 2,749 participants in the Coronary Artery Risk Development in Young Adults (CARDA) study. Participants completed respiratory symptom questionnaires at baseline and at 2 years, then underwent spirometry on multiple occasions during 30 years' follow-up. Relationships between baseline symptoms and later changes in lung function, incident obstructive and restrictive lung physiology, and CT evidence of emphysema were assessed.

In models assessing all three outcomes, the main predictors were symptoms related to cough or phlegm, episodes of bronchitis, wheezing, shortness of breath, and chest illnesses at both baseline and year 2. With adjustment for covariates – including body mass index, asthma, and smoking – any patient-reported pulmonary symptom was associated with a 2.71 mL/yr excess decline in FEV_1 and a 2.18 mL/yr decline in FVC. Pulmonary symptoms in young adulthood were also associated with increased odds of developing (prebronchodilator) obstructive physiology, odds ratio (OR) 1.63; and restrictive physiology, OR 1.40; Participants with cough-related symptoms were more likely to develop CT evidence of emphysema: OR 1.56.

In a population of generally healthy young adults, respiratory symptoms from the late teens to early thirties are associated with faster decline in lung function and a higher risk of incident COPD. Symptoms related to cough or phlegm and episodes of bronchitis are linked to later development of radiographic emphysema. The researchers conclude, "[I]dentification of individuals with sustained respiratory symptoms in routine clinical practice could be helpful for identification of individuals at greatest risk for future lung disease."

COMMENT: The study of young adults from the CARDIA Lung study gives us insight into the importance of respiratory symptoms early in life. Although such symptoms predict a modest drop in FEV_1, certain features in utero and ex utero may contribute to persistent symptoms. For example, cough-related symptoms are associated with obstructive lung physiology and emphysema whereas shortness of breath is associated with restrictive lung physiology. These factors may be present at any stage of life including premature birth, tobacco smoke exposure, childhood respiratory infections, and occupational exposures. These should be investigated in all of our patients. Preserving lung health involves a combination of avoiding environmental and smoke exposure, early and adequate treatment of atopy in asthma patients, and vaccination against seasonal influenza. See also the editorial by Bhatt (Am J Respir Crit Care Med. 2018;197:1521-1523).

B.E.C.

Kalhan R, Dransfield MT, Colangelo LA, et al: Respiratory symptoms in young adults and future lung disease: the CARDIA Lung Study. Am J Respir Crit Care Med. 2018;197:1616-1624.

Keywords: COPD, emphysema, lung function, respiratory symptoms

Can Basophil Proteins Predict Response to Omalizumab in CIU?

The mechanisms of omalizumab's effectiveness in controlling symptoms of chronic idiopathic urticaria (CIU) remain unclear. Previous studies have reported basophil changes after omalizumab treatment. This study examined the basophil proteome in patients with CIU and its possible relationship to omalizumab responsiveness.

The open-label study included 7 patients with persistent CIU receiving one to four monthly doses of omalizumab. Four patients had clinically significant symptom improvement, three of them after the first dose. The researchers performed proteomic analysis of basophils collected at baseline, looking for differences between the omalizumab responders and nonresponders. Three controls without urticaria were studied as well.

A total of 322 basophil proteins were measured more than twice in at least two patients in each experimental group. Of these, 30 proteins were found only in omalizumab responders, 196 only in nonresponders, and 96 in both groups. Intermediate filament proteins and cytoskeletal or adhesion proteins each accounted for 8 of the 30 proteins found exclusively in responders. Three percent of all proteins found in CIU patients were not present in controls.

Proteomic analysis of basophils in patients with CIU shows evidence of a response to cellular stress. In this small sample, the specific pathways identified appear different for omalizumab responders versus nonresponders. Understanding the basophil proteome in CIU might lend insights into the pathophysiology of this condition.

COMMENT: This proof-of-concept study analyzed proteins in basophils from 7 patients with CIU treated with omalizumab. Unfortunately, 2 of 3 nonresponders only received 1 to 2 months of therapy and thus could still have had a delayed response. About 10% of assessed proteins were seen only in responders but not in other patients or in the 3 controls. Basophil proteomics is certainly a novel approach, but additional studies in larger populations with better-defined response patterns are needed before any meaningful conclusions can be made.

D.A.K.

Stitt JM, Dzieciatkowska M, Edwards MG, et al: The basophil proteome in chronic spontaneous urticaria distinguishes responders to omalizumab from non-responders. Clin Exp Allergy. 2018;48:898-901.

Keywords: basophils, chronic idiopathic urticaria, omalizumab, proteomics

Beta-Blockers Are Safe in COPD

Physicians may hesitate to use β-blockers in patients with chronic obstructive pulmonary disease (COPD), despite studies suggesting that these medications can reduce COPD exacerbations and mortality. Data from a series of studies evaluating the tiotropium/olodaterol combination in patients with moderate to very severe COPD were used to compare outcomes for patients who were and were not taking β-blockers.

The post hoc analysis included 5,162 patients with GOLD II to IV COPD participating in the TONADO studies. Of these, 577 patients (11%) were taking β-blockers at baseline. Lung function changes, patient-reported outcomes, and safety parameters were compared for patients with and without β-blocker treatment.

At baseline, COPD patients taking β-blockers had a higher postbronchodilator FEV_1 (1.470 versus 1.362 L) and were more likely to have a history of cardiovascular disease. Lung function improved from baseline in patients who were and were not taking β-blockers, with both groups showing improvement in dyspnea. Respiratory adverse events, particularly COPD events, were slightly more frequent in patients not receiving β-blockers. Time to first COPD exacerbation was similar between groups. The overall rate of serious adverse events was 19.4% in the β-blocker group, compared to 16.0% for patients not taking β-blockers. Respiratory status and the safety of the study treatment were unaffected by β-blocker treatment.

The findings suggest that, in patients with moderate to very severe COPD, β-blocker treatment does not adversely affect lung function, respiratory status, or dyspnea symptoms. The higher rate of serious adverse events in patients taking β-blockers may reflect the higher overall comorbidity in this group. The study supports recommendations to continue β-blocker use, when clinically indicated, in patients with COPD.

COMMENT: This 12-month study evaluated COPD patients from phase 3 studies of a long-acting muscarinic/β_2-adrenergic agonist combination. Eleven percent of patients were taking β-blockers. This group showed no significant differences in outcomes including lung function, time to exacerbation, dyspnea, or quality of life, compared to patients not taking beta-blockers. The study adds to the literature (including many short-term studies) supporting the safety of β-blockers in COPD and concluding that these drugs do not attenuate the beneficial effects of LABA-based therapies.

D.A.K.

Maltais F, Buhl R, Koch A, et al: β-Blockers in COPD: a cohort study from the TONADO research program. Chest. 2018;153:1315-1325.

Keywords: beta-blockers, COPD

Aspirin Prevents Emphysema, Maybe

Chronic obstructive pulmonary disease (COPD) is associated with increased platelet activation, suggesting a possible role of platelets in emphysema and COPD. Data from a follow-up study including serial computed tomography (CT) scans were used to assess the effects of regular aspirin use on progression of emphysema.

The analysis included 4,257 participants from the Multi-Ethnic Study of Atherosclerosis, aged 45 to 84 years and free of clinical cardiovascular disease at baseline. Mean age at baseline was 61 years; 54% of participants had a history of smoking.

Participants underwent a series of cardiac (2000-07) and full-lung (2010-12) CT scans over 10 years of follow-up. "Percent of emphysema" was assessed based on the percentage of emphysema-like lung less than –950 Hounsfield units. At baseline, 22% of participants reported regular aspirin use (3 or more days per week). The relationship between regular aspirin use and progression of emphysema-like lung was assessed.

Over 10 years, percentage of emphysema-like lung increased by 0.60 percentage points. Progression was significantly slower for regular aspirin users, with a difference of –0.34% in the fully adjusted model. The effect on emphysema progression was unaffected by aspirin dose but was greater in participants with airflow limitation, and possibly among men and current smokers. Aspirin use was unrelated to changes in lung function.

The results suggest slower progression of emphysema-like CT changes in the lung in regular aspirin users. Although the effect appears modest, it may still be relevant to disease progression. Further studies of platelet activation and aspirin in COPD and emphysema are warranted.

COMMENT: This was a well-designed study of a large group of patients of varying ethnicity who underwent serial CT imaging of the heart and lungs. Subjects at baseline who took any dose of aspirin regularly had a 50% reduction in progression of emphysema over 10 years. That sounds impressive until you look at the magnitude of the change, which was a paltry 0.3%. While the authors suggest their findings "may" still be clinically relevant, this seems unclear. Nevertheless, the results were stronger among current smokers; perhaps a higher-risk population would have shown more impressive results.

D.A.K.

Aaron C, Schwartz JE, Hoffman EA, et al: A longitudinal cohort study of aspirin use and progression of emphysema-like lung characteristics on CT imaging: the MESA Lung Study. Chest. 2018;154:41-50.

Keywords: aspirin, COPD, emphysema

Pediatric EoE: Risk and Protective Factors

Environmental factors during early life seem to contribute to the rising incidence of eosinophilic esophagitis (EoE). Prenatal, intrapartum, and postnatal factors associated with the development of pediatric EoE were assessed in a case-control study.

The study included the mothers of 127 children with EoE and 121 community controls, using a children's hospital database. Responses to an online questionnaire were used to evaluate a wide range of possible early-life determinants for EoE.

Prenatal factors associated with the development of EoE included maternal fever, adjusted odds ratio (OR) 3.18; and preterm labor, OR 2.18. The only significant intrapartum factor was cesarean delivery, OR 1.77. Postnatal risk factors included use of antibiotics, OR 2.30, and use of acid suppressants, OR 6.05. Having a furry pet during infancy was a significant protective factor: OR 0.58. Breastfeeding or maternal use of multivitamin or folic acid supplements were unrelated to EoE.

The study suggests several early-life factors associated with an increased risk of pediatric EoE. Pet exposure during infancy appears to be a protective factor. Further efforts are needed to clarify the role of early-life exposures in the pathogenesis of EoE.

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

S.M.F.

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

Keywords: EoE, prevention, risk factors

Idiopathic Anaphylaxis: Where's the Beef?

Patients who become sensitized to galactose-α-1,3-galactose (alpha-gal), occurring via previous tick bites, can develop delayed anaphylaxis after eating red meat. The authors report several cases of alpha-gal sensitivity identified in a series of patients with idiopathic anaphylaxis.

Seventy patients referred for evaluation of idiopathic anaphylaxis were screened for specific IgE to alpha-gal. Testing identified 6 men, aged 41 to 70 years, with alpha gal-specific IgE above the cutoff level of 0.35 IU/mL. All patients had non-B blood types and lived within the distribution of the lone star tick, *Amblyomma americanum.* All had eaten red meat within 3 to 6 hours before the onset of anaphylaxis symptoms.

Two patients were found to have indolent systemic mastocytosis. They had more severe clinical reactions, despite having lower specific IgE and higher serum tryptase levels. All patients remained free of further episodes of anaphylaxis after starting a diet free of red meat.

In a referral series of patients with idiopathic anaphylaxis, 9% had alpha-gal sensitivity. Routine screening for specific IgE to alpha gal is recommended, especially for patients who live in areas where the lone star tick is present and who have delayed anaphylactic reactions.

COMMENT: Alpha-gal syndrome merits consideration in the evaluation of patients with unexplained anaphylaxis – particularly those who reside in or have traveled to geographic areas within the distribution of the lone star tick, and who have exhibited a pattern of late-night anaphylaxis.

D.M.L.

Carter MC, Ruiz-Esteves KN, Workman L, et al: Identification of alpha-gal sensitivity in patients with a diagnosis of idiopathic anaphylaxis.
Allergy. 2018;73:1131-1134.

Keywords: alpha-gal sensitivity, anaphylaxis, food allergy, red-meat allergy

REVIEW OF NOTE

COMMENT: This is a position paper from the American Thoracic Society regarding the diagnosis of primary ciliary dyskinesia. It discusses the genetic basis of this disease, formulation of the diagnostic algorithm, and appropriate evaluation of the patient.

B.E.C.

Shapiro AJ, Davis SD, Polineni D, et al: Diagnosis of primary ciliary dyskinesia: an official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;197:e24-e39.