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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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OUR 20TH YEAR -OUR FIRST SPECIAL 'MOC' ISSUE

This year marks the twentieth anniversary of AllergyWatch. Since our first issue in 1998 - edited by Dr. Emil J. Bardana and later by Dr. Anthony Montanaro - we have strived to present concise updates and commentaries on new research and important new developments in allergy and immunology.

This issue marks a new feature that we think will prove to be of high value to our specialty as we align with the American Board of Allergy and Immunology's new Maintenance of Certification (MOC) program. Two special issues per year will cover the papers included in the semiannual ABAI examinations. The usual brief summaries are accompanied by commentaries written by our panel of Assistant Editors, followed by reference citations for each paper.

The article summaries and editor comments provided are not endorsed by the publishers, authors, or the American Board of Allergy & Immunology (ABAI), and therefore do not represent their views. The sole purpose of these summaries is to provide diplomates with an overview of content relevant to the ABAI's new Continuous Assessment Program (CAP). S.A.T. & C.D

Our 20th Year - Our First Special 'MOC' Issue

Head and Neck	1
Dermatology	3
Lung	4
Food/Drug	6
Anaphylaxis	7
Hypersensitivity Disorders	9
Immunodeficiencies 1	0
Eosinophilia/Gastrointestinal 1	1

2018 Editor-in-Chief Disclosure:

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Head and Neck

Approval of new sublingual immunotherapy (SLIT) products in the United States was based on large clinical trials, supported by years of experience in Europe. This PRACTALL consensus report addresses practical issues related to clinical use of SLIT for grass and ragweed allergy.

Listed indications for SLIT include pollen-induced allergic rhinitis, with or without conjunctivitis. None of the approved products include asthma alone as an indication, although pivotal trials showed benefits in terms of asthma symptoms. Sublingual and subcutaneous immunotherapy are both effective, with insufficient evidence to compare the two routes. Clinically, SLIT is at least as good as as-needed medications, with the advantage of being a disease-modifying approach.

The report identifies effective dose regimens for SLIT; if patients forget a dose, they should take it the following day. Available evidence suggests that dual administration of SLIT products is well tolerated. Local adverse events reactions to SLIT usually resolve without any medical intervention, while serious systemic reactions appear less common than with subcutaneous immunotherapy. Evidence supports the safety and efficacy of SLIT in children and adolescents.

Trials report that clinical and immunologic benefits persist for at least 2 years after 3 years of active SLIT. In children, SLIT for allergic rhinitis might reduce future asthma risk. While treatment is always individualized, SLIT may be appropriate for patients who prefer a disease-modifying approach and those who do not have a good response to standard medications. As with subcutaneous immunotherapy, adherence to SLIT outside of research settings is relatively poor. Several strategies to enhance SLIT adherence have been identified.

COMMENT: Three FDA-approved SLIT products—Grastek, Oralair, and Ragwitek—are described in this article. (The house dust mite HDM preparation Odactra is not described.) Although classic allergy immunotherapy leads to a better response, SLIT plays a role in selected patients who are not able to attend allergy immunotherapy in the healthcare setting or who have an aversion to injections. This parameter gives direction for use and expected outcomes with SLIT. There is suggestion that disease modification may occur when SLIT is continued for at least 3 years

B.E.C.

Li JT, Bernstein DI, Calderon MA, et al: Sublingual grass and ragweed immunotherapy: clinical considerations—a PRACTALL consensus report. J Allergy Clin Immunol. 2016;137:369-376.

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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
- IAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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Dupilumab, a human monoclonal antibody against interleukin (IL)-4 receptor alpha, inhibits signaling of the type 2 cytokines IL-4 and IL-13. It has shown clinical efficacy in patients with asthma and atopic dermatitis. This randomized trial evaluated the effects of add-on dupilumab for chronic sinusitis and nasal polyposis.

The multicenter trial included 60 adults with chronic sinusitis and nasal polyposis who had an inadequate response to intranasal corticosteroid. Thirty-five patients had comorbid asthma. All patients received mometasone furoate nasal spray for 16 weeks. In addition, they were randomly assigned to subcutaneous dupilumab, a 600 mg loading dose followed by 300 mg/week, or placebo. The primary outcome was change in 0-to-8 endoscopic nasal polyp score during treatment.

Least-square (LS) mean change in nasal polyp score was –1.9 in the dupilumab group versus –0.3 with placebo. Secondary outcomes also favored dupilumab, including the Lund-Mackay computed tomography score, LS mean difference –8.8; SinoNasal Outcome Test, LS mean difference –18.1; and University of Pennsylvania Smell Identification Test, LS mean difference 14.8. Dupilumab was associated with reductions in biomarkers of type 2 helper T cells, including eotaxin-3, thymus and activation-regulated chemokine (TARC), and IgE. Injection site reactions were more frequent with dupilumab than placebo.

Adding dupilumab to intranasal corticosteroids reduces nasal polyp burden in adults with refractory chronic sinusitis and nasal polyposis. The authors call for further studies of dupilumab as adjunct therapy or compared to other medications or surgery.

COMMENT: Nasal polyposis with chronic sinusitis has been associated with Th2 inflammation, although patients may not have clinically significant IgE-mediated sensitivity. This proof-of-concept study suggests that using dupilumab to block the IL-4 receptor α subunit—thereby inhibiting the IL-4 and IL-13 pathways—can be helpful clinically in patients with nasal polyposis. The study is important since it not only suggests that the immunologic mechanism for nasal polyposis is mediated by Th2 inflammation but also that blocking this pathway could have clinical benefit.

S.M.F

Bachert CL, Mannent RM, Naclerio RM, et al: Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis. JAMA. 2016;315:469-479.

Introposal triansingloss is commonly used for

Intranasal triamcinolone is commonly used for the treatment of allergic rhinitis in pregnant women. Although it is classified as a "pregnancy category C" product, there are no previous data on intranasal triamcinolone in human pregnancies. This issue was addressed in a population-based prospective cohort study.

Using data from the Quebec Pregnancy Cohort, the researchers identified 2,498 women exposed to intranasal corticosteroids during the first trimester of pregnancy. This included 296 women exposed to triamcinolone, 2,180 exposed to other corticosteroids, and 22 exposed to triamcinolone plus other corticosteroids. Outcomes were compared to those of 140,654 nonexposed women. The outcomes of interest were major congenital malformations, small-for-gestational-age (SGA) status, and spontaneous abortions.

On adjusted analysis, first-trimester exposure to intranasal triamcinolone was not significantly associated with the risk of overall congenital malformations. However, the exposed group did have a • • • higher risk of respiratory system defects: odds ratio (OR) 2.71. Intranasal triamcinolone risk was not associated with the risk of spontaneous abortion. Based on 50 exposed cases, second- or third-trimester exposure to triamcinolone was unrelated to the risk of SGA pregnancy.

Treatment with intranasal triamcinolone during pregnancy is not associated with an increased overall risk of major congenital malformations, spontaneous abortion, or SGA status. There is a possible increase in respiratory defects in triamcinolone-exposed cases, although this might be a chance finding. The findings may help to inform decisions about the use of intranasal triamcinolone, which is available over-the-counter, to treat the common problem of allergic rhinitis during pregnancy.

COMMENT: In 2004, the FDA upgraded intranasal budesonide from category C to category B in pregnancy, based on safety data from 3 Swedish birth registry studies. All other intranasal corticosteroids have remained category C. In the case of triamcinolone, intramuscular use has been found to be teratogenic in animals. Up until this study, there have been no data regarding intranasal triamcinolone use in pregnancy. The population-based cohort study used data from four large databases in Quebec. The researchers found overall no statistically significant increased risk of major congenital malformations, SGA, or spontaneous abortions associated with intranasal triamcinolone use in pregnancy. Similar outcomes were seen with other intranasal corticosteroids. It should be noted, however, that first-trimester use of intranasal triamcinolone was associated with significant increased risk of respiratory system defects (malformations of the larynx, trachea, bronchus and choanal atresia), which is similar to findings in rats. Furthermore, the rate of respiratory defects increased over time during the study, coinciding with an increase in use of intranasal triamcinolone during pregnancy. As noted by the authors, although this drug is available over the counter, providers should be aware of the potential risk of respiratory defects when used during the first trimester of pregnancy. This article provides a wonderful resource when discussing the potential risk of use of nasal triamcinolone during pregnancy.

J.J.O.

Bérard A, Sheehy O, Kurzinger M-L, Juhaeri J: Intranasal triamcinolone use during pregnancy and the risk of adverse pregnancy outcomes. J Allergy Clin Immunol. 2016;138:97-104.

Dermatology

Advances in therapy for atopic dermatitis (AD) will require new insights into the pathogenesis of this complex condition. The authors review recent advances in the epidemiology, pathology, diagnosis, and treatment of AD.

Recent studies suggest a stable incidence of AD among children in Northern Europe; risk factors for AD in infancy include adiposity and maternal atopy. Interactions with systemic disorders include increased risks of rheumatoid arthritis and inflammatory bowel disease, but a decreased risk of type 1 diabetes. An "inflammatory skin march" mediated by interleukin-1 may explain the increased cardiovascular risk in patients with AD or psoriasis.

Genome-wide association studies have identified novel gene associations with AD. Several susceptibility local for the "atopic march" in children with AD have been reported as well. Several lines of evidence point to altered or dysregulated balance of T-cell immunity in patients with AD. Measurement of transepidermal water loss in newborns and evaluation of the gut microbiome have been identified as possible prognostic tools. Methods using laser capture microdissection of skin samples might lead to development of new diagnostic tests for AD.

One recent study demonstrated the inflammatory effect of pollen on exposed AD skin, highlighting the importance of avoiding aeroallergen exposure. Evidence suggests that prebiotics have a preventive effect against early AD, although this is not sustained in low-risk infants. Recent studies have examined several approaches to promoting recovery of the skin barrier in AD—including conventional means such as petrolatum and UVB and molecular approaches targeting Janus kinase, signal transducer and activator of transcription 3, extracellular signal-regulated kinase, sirtuin 1, or aryl hydrocarbon receptor. Dupilumab and other biologic therapies are being actively investigated.

At present, treatments for AD are directed toward improving and controlling symptoms. Further research into the mechanism of barrier damage and immune dysregulation may lead to the development of more specific approaches to AD prevention and control.

COMMENT: This review highlights recent advances in atopic dermatitis. Most of the review focuses on key developments that have improved our understanding of AD: pathophysiologic mechanisms, immunophenotyping, current and possible future therapies, biomarkers, and the importance of cutaneous and gastrointestinal dysbiosis. D.M.L.

Nomura T, Kabashima K: Advances in atopic dermatitis in 2015. J Allergy Clin Immunol. 2016;138:1548-1555. •

The previous practice parameter on contact dermatitis (CD) focused on the basics of this condition and the use of patch testing. Since then, advances have occurred in many areas, including the use of the TRUE Test patch test method and increased understanding of type IV hypersensitivity reactions. This document provides an updated practice parameter on CD, addressing recent advances in scientific understanding and clinical management.

The 2015 update includes 45 summary statements addressing current diagnosis and management of CD. The diagnosis of allergic CD should be considered in patients with chronic dermatitis, eczematous or noneczematous. Patch testing is the gold standard for diagnosis; evaluation of contact allergens should include home and work • • •

exposures as well as irritant and allergic causes. Considerations for patients with various clinical presentations are identified.

A series of recommendations addresses general principles for patch testing, which should be interpreted in light of the patient's clinical and exposure history. Recommendations for sources of exposure to clinically relevant allergens include seasonal pollen allergens, cosmetics and hygiene products and the chemicals they contain. The use of patch testing for diagnosis of CD due to topical medications is addressed, as well as pediatric and occupational CD. Summary statements related to treatment include counseling to avoid the allergen or irritant, appropriate adjunct treatments, and education for patients with occupational CD.

Each recommendation is rated according to the strength of the supporting evidence. The 2015 update is intended to provide "practical, clinically pertinent, and user-friendly" information to address important clinical questions regarding allergic or irritant CD.

COMMENT: Since allergists are seeing more dermatologic conditions, staying up-to-date on contact dermatitis is important to clinical practice. This parameter covers many new areas and covers additional important contact allergens since the prior 2006 parameter. Some of the new areas include preoperative screening for metal implants, baboon syndrome, and drug patch testing. Additional important allergens discussed in this update include methychloroisothiazolinone and methylisothiazolinone, cocoamidopropyl betaine, and essential oils.

D.A.K.

Fonacier L, Bernstein DI, Pacheco K, et al: Contact dermatitis: a practice parameter–update 2015.

J Allergy Clin Immunol Pract. 2015;3:S1-S39.

In March 2017, the FDA approved the interleukin-4 (IL-4) receptor alpha antagonist dupilumab for treatment of moderate to severe atopic dermatitis (AD) in adults. This paper reports the results of the pivotal SOLO 1 and SOLO 2 trials of dupilumab for AS.

The randomized, placebo-controlled trials enrolled adults with moderate to severe AD that was inadequately controlled by topical medications: 671 patients in SOLO 1 and 708 in SOLO 2. The intervention groups received 16 weeks of treatment with dupilumab, 300 mg weekly or alternating with placebo every other week. The primary outcome was a score of 0 or 1 on the Investigator's Global Assessment, indicating clear or almost clear of AD; plus at least a 2-point reduction in the same score from baseline to 16 weeks.

In the combined studies, the primary outcome was reached in 37% of patients with weekly dupilumab and 38% with dupilumab every other week, compared to 10% with weekly placebo. The dupilumab groups were more likely to achieve at least 75% improvement in the Eczema Area and Severity Index. Dupilumab also improved secondary outcomes including pruritus, sleep, anxiety and depression symptoms, and health-related quality of life. The main adverse effects were injection site reactions and conjunctivitis.

The SOLO 1 and 2 trials show significant clinical benefits of 16 weeks of dupilumab therapy, weekly or every other week, in adults with moderate to severe AD inadequately controlled by topical medications. In addition to AD signs and symptoms, dupilumab improves mental health and quality of life outcomes. Further studies are needed to establish dupilumab's long-term safety and effectiveness.

COMMENT: Patients with moderate to severe AD have been treated with topical agents that have lacked efficacy and/or systemic medications that have posed risk for toxicity. These two independent randomized controlled trials demonstrate the therapeutic utility of dupilumab in adults with moderate to severe AD. Focusing on the primary outcome, the proportion of subjects with an investigator's global assessment score of "clear or almost clear," the number needed to treat associated with randomization to dupilumab compared to placebo is 3.6. This is a very favorable treatment profile for a condition previously associated with unmet needs and impaired quality of life.

D.M.L.

Simpson EL, Bieber T, Guttman-Lasky E, et al: Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375:2335-2348.

Lung

Sublingual immunotherapy (SLIT) can improve clinical outcomes for patients with allergic rhinitis due to house dust mite (HDM). This trial evaluated the effects of SLIT on exacerbation rate among patients with HDM allergy-related asthma.

The randomized, multicenter European trial included 834 adults with HDM allergy causing asthma that was not well controlled by treatment including inhaled corticosteroids (ICS). The study excluded patients with FEV_1 of less than 70% predicted or asthma hospitalization within the previous 3 months. Patients were assigned to daily treatment with placebo or HDM SLIT, 6 or 12 SQ. The primary outcome was time to first moderate to severe exacerbation, assessed during 3-month periods of ICS dose reduction and withdrawal.

In 693 patients who completed the study, HDM SLIT was associated with a significant reduction in exacerbation rate: hazard ratio (HR) 0.72 at the 6 SQ dose and 0.69 at the 12 SQ dose, compared to placebo. Absolute risk differences were 0.09 and 0.10, respectively. Both HDM SLIT doses were associated with a reduced risk of exacerbation with deterioration in asthma symptoms and an increase in HDM-specific IgG4. Active SLIT had no significant effect on asthma control or asthma-related quality of life.

There were no severe systemic reactions. Mild to moderate oral pruritus occurred in 13% of the 6 SQ-HDM group, 20% of the 12 SQ-HDM group, and 3% of the placebo group.

In adults with HDM allergy-related asthma, HDM • • •

SLIT reduces moderate to severe exacerbations during a period of ICS dose reduction. Absolute risk decreases by 9 to 10 percentage points, mostly due to fewer moderate exacerbations. Long-term safety and efficacy studies are needed.

COMMENT: This study looks at two doses of HDM in the treatment of adults with asthma over an 18-month period. Of these patients, 72% had poorly controlled asthma and 28% had very poorly controlled asthma. All had FEV₁ over 70% of predicted. Patient selection is key, as it is difficult to impute HDM to be causally related in a particular patient's asthma. There was no difference in HDM SLIT response in polysensitized versus monosensitized patients. Importantly, this study reported a reduction in moderate asthma exacerbations. The exacerbations did not require prednisone and may have been amenable to more aggressive bronchodilator therapy. Treatment-related adverse events were common, including both gastrointestinal and upper airway irritation being observed. Further studies are needed to assess longterm efficacy and safety, but SLIT may be an appropriate intervention for selective patients.

B.E.C.

Virchow JC, Backer V, Kuna P, et al: Efficacy of house dust mite sublingual allergen immunotherapy tablet in adults with allergic rhinitis. JAMA. 2016;315:1715-1725. •

Identification and validation of biomarkers will play a critical role in developing precision medicine approaches to asthma. This article reviews progress in identifying biomarkers to direct treatment decision-making in asthmatic patients.

The authors review evidence on four emerging asthma biomarkers, all of which are mainly relevant to patients with a"Th2-high" disease pattern. Eosinophils have been identified as a biomarker for asthma exacerbations, but only when they persist in the sputum or peripheral blood despite corticosteroid treatment, in patients without disease control. Sputum eosinophils are a more reliable marker than blood eosinophils, but sputum eosinophil measurement may be impractical. A peripheral blood eosinophil count of 150/mm³ or higher has emerged as a threshold for benefit from mepolizumab therapy, although this has not been firmly established.

Many studies have evaluated exhaled nitric oxide as a marker of Th2 inflammation, but its use in clinical practice is "complex and nuanced." Exhaled NO and sputum eosinophils are equally effective in predicting responses to omalizumab and mepolizumab. Pending further study, exhaled NO is a promising test for use in patients with more severe asthma and those being considered for biologic therapies.

Periostin, measured in bronchoalveolar lavage fluid, may identify patients with Th2-high asthma who will have a good FEV₁ response to inhaled corticosteroids. High periostin may also identify patients with an interleukin-13-dependent T2 phenotype who are more likely to respond to lebrikizumab.

Higher serum IgE is correlated with asthma severity in

both adults and children. In children, higher antigen-specific IgE may reflect a Th2 profile. However, IgE level does not necessarily predict the benefits of omalizumab. In contrast, exhaled NO, peripheral blood eosinophils, and periostin may all be independent predictors of omalizumab response.

COMMENT: The use of biomarkers has revolutionized the ability to apply precision medicine to asthma care. Although we still do not have reliable low-Th2 biomarkers, there is evidence to support the use of biomarkers in high-Th2 patients. The eosinophil is believed to reflect airway injury and contribute to airway hyperreactivity and remodeling. The finding of eosinophils at 300 or greater has been shown to correlate with sputum eosinophils in most patients and predicts a higher risk of exacerbations. Exhaled nitric oxide is a surrogate biomarker of eosinophilic airway inflammation. Levels of greater than 50 ppb in adult asthma describe a group of patients who are likely to respond to inhaled steroid. Persistent elevated levels despite moderate to high doses of inhaled steroid describe a group of patients who are at increased risk for exacerbations, especially when the eosinophil count is over 400. The correlation with sputum eosinophils is 70%. When both total and specific IgE are elevated, this is a marker of disease severity. Total IgE is also needed to establish omalizumab dose and screen for allergic bronchopulmonary mycosis. At present, biomarkers help define disease activity and lead to application of biologic treatment, but this field is in constant flux.

B.E.C.

Berry A, Busse W: Biomarkers in asthmatic patients: has their time come to direct treatment? J Allergy Clin Immunol. 2016:137:1317-1324.

Higher exposure to traffic-related air pollution (TRAP) is associated with reduced lung function and an increased risk of allergic respiratory diseases in children. Less is known about the respiratory effects of air pollution in adults. This study assessed the effects of TRAP exposure on asthma and other respiratory outcomes among adults residing in a lowpollution area.

The analysis included subjects from the Tasmanian Longitudinal Health Study, enrolled as children in 1968. As adults in their forties, 1,405 participants underwent skin prick and lung function testing. Each subject's mean annual residential nitrogen oxide exposure was estimated based on current residential address. Associations of TRAP exposure with allergic sensitization, lung function, wheezing, and asthma were assessed.

Adults with higher NO₂ exposure were at increased risk of atopy, adjusted odds ratio (OR) 1.14 per interquartile range increase; and current wheezing, OR 1.14. Those who lived within 200 m of a major road were at higher risk of atopy, OR 1.26; and current wheezing, OR 1.38. Subjects living near a major road had lower lung function, including pre- and postbronchodilator FEV₁ and prebronchodilator forced expiratory flow at 25% to 75% of forced vital capacity.

Living near a major road interacted with the gluthathione S-transferase gene to affect the risk of asthma and • • •

allergic disease outcomes. Carriers of the *GSTT1* null genotype were at increased risk of atopy, asthma, and atopic asthma with higher TRAP exposure.

Even relatively low levels of TRAP exposure are associated with atopy, asthma, and reduced lung function in middleaged adults. These risks appear particularly high in individuals with the *GSTT1* null genotype. This finding may have important public health implications for a genetically susceptible population.

COMMENT: As noted in studies done in children in Southern California, there is evidence that even low levels of TRAP in adults can lead to increased airway hyperreactivity and asthma. This is amplified for those living within 200 meters of a heavily traveled road or having variants of glutathione Stransferase genes. The present study is the first to show this association in adults. The data are so similar to previous studies in children that biological plausibility is much stronger. These are important features as related to urban planning and effects of global warming.

B.E.C.

Bowatte G, Lodge CJ, Knibbs LD, et al: Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age. J Allergy Clin Imunol. 2017;139:122-129.

Food/Drug

New treatments for food allergies have emerged over the past decade, including oral, sublingual, and epicutaneous immunotherapy. The authors review the current status and future potential for these food allergy immunotherapy approaches.

Oral immunotherapy (OIT) generally consists of initial dose escalation, typically in a single day, followed by gradual dose buildup, then a prolonged maintenance phase. Most patients who tolerate therapy reach a significant level of desensitization. However, many patients do not achieve sustained unresponsiveness at follow-up. Representative studies of OIT to peanut, egg, and milk are discussed. Clinical use of these approaches has been limited by the substantial numbers of patients who cannot tolerate OIT.

Several studies have evaluated sublingual immunotherapy approaches (SLIT), mainly to peanut. Double-blind placebo-controlled trials have suggested that peanut SLIT offers "a modest level of desensitization," with good safety outcomes. However, a minority of patients completed 3 years of treatment and few achieved sustained unresponsiveness. A few comparative trials have reported that OIT is more effective, but carries a higher rate of adverse reactions than SLIT.

Preclinical studies have suggested that epicutaneous immunotherapy (EPIT) using an allergen-containing patch is a promising approach. Studies of EPIT to milk and peanut are ongoing. Modified allergen immunotherapy approaches such as "peptide immunotherapy" are being evaluated as well. Several potential adjunctive therapies have been studied, with studies of omalizumab reporting improved safety outcomes.

Important questions for the future include the optimal response to food allergy immunotherapy. Goals may differ between patients and foods; particularly for peanut, even low-level protection might be an acceptable outcome. While OIT and SLIT are already being used in clinical settings, the author writes, "Personally, I firmly believe that many issues need to be addressed before food immunotherapy should be used in clinical practice."

COMMENT: In this excellent 2016 review of food immunotherapy, the data show that OIT is the most efficacious therapeutic option compared to SLIT and EPIT, although even with OIT only about 50% of patients achieved sustained unresponsiveness after stopping maintenance. Oral immunotherapy also has more adverse reactions, with 10% to 36% withdrawing from the trials because of adverse events. All forms of food immunotherapy showed immunologic changes consistent with our usual SCIT. However, in terms of efficacy, OIT > SLIT > EPIT. The author suggests that therapeutic goals may differ between patients and foods, but he does state that many issues need to be addressed before food immunotherapy should be used in general clinical practice.

S.M.F.

Wood RA: Food allergen immunotherapy: current status and prospects for the future. J Allergy Clin Immunol. 2016;137:973-982.

The LEAP study has confirmed that early dietary introduction of peanut has a benefit in preventing peanut allergy. However, for other food allergens, the benefits of early introduction remain unclear. This randomized trial evaluated the effects of early introduction of common food allergens in a general population of breast-fed infants.

The study included 1,303 infants who were exclusively breast-fed when enrolled at age 3 months. One group received early introduction of six common food allergens: peanut, cooked egg, cow's milk, sesame, whitefish, and wheat. Control infants continued on exclusive breast-feeding to about age 6 months. Development of food allergy was assessed when the children were 1 to 3 years old.

On intention-to-treat analysis, there was no significant difference in the percentage of children developing one or more food allergies: 5.6% in the early introduction group and 7.1% in the control group. On per-protocol analysis, the difference was larger, 2.4% versus 7.3%; with significant reductions in peanut allergy, zero versus 2.5%; and egg allergy, 1.4% versus 5.5%.

The reductions in peanut and egg allergy were significant for children who consumed 2 g per week of those food proteins. Adherence to early introduction was low; there were no cases of anaphylaxis and no problems related to breastfeeding or growth.

Analyzed by intention to treat, the trial finds no significant reduction in food allergies with early introduction of multiple potentially allergenic foods. Per-protocol analysis sug- • • •

gests possible reductions in peanut and egg allergy with early introduction. The protective effects of early introduction may depend on dose and adherence.

COMMENT: Patients want to know how to "prevent" food allergy. Based on the landmark LEAP study, infant feeding recommendations have changed. In this "Enquiring About Tolerance" (EAT) Study, early introduction of multiple allergenic foods in 3-month-old infants was safe. Per-protocol analysis suggested possible decreases in peanut and egg allergy with early introduction, but these findings were not as promising as the LEAP results. The authors remind us that protective effects are likely related to both adherence (which was low) and dose. Time will tell if early introduction will decrease the incidence of food allergy.

V.H.-T.

Perkin MR, Logan K, Tseng A, et al: Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016;374:1733-1743.

The first US clinical guidelines for diagnosis and management of food allergy, published in 2010, did not include strategies for prevention of peanut and other food allergies. Since then, the LEAP trial has found that early introduction of peanut can reduce the risk of childhood peanut allergy. This prompted an addendum to the guidelines addressing the prevention of peanut allergy.

Prepared by an expert panel, the addendum includes three new guidelines. Based on moderate-quality evidence, introduction of age-appropriate peanut-containing foods at age 4 to 6 months is recommended for infants with severe eczema, egg allergy, or both. Peanut-specific IgE (sIgE) measurement and/or skin-prick testing should be "strongly considered" before peanut introduction. Specialist referral is recommended for children with an ImmunoCAP sIgE level of 0.35 kU_A/L or greater. The addendum also defines three categories for interpreting the results of skin-prick testing.

Peanut introduction around age 6 months is recommended for infants with mild to moderate eczema. In these cases, peanut may be introduced at home, without in-office evaluation. Peanut may be freely introduced, along with other foods, in infants without eczema or food allergy. For the latter two recommendations, the quality of evidence is low.

Recent clinical trials support early introduction of peanutcontaining foods into the diet of infants at various levels of risk for peanut allergy. The addendum includes instructions for peanut introduction at home or in office settings.

COMMENT: The landmark LEAP trial, published in 2015, provided solid evidence that early introduction of peanut to high-risk infants reduced their risk of development of peanut allergy. Implementation in clinical practice has been slow, and many allergists are uncertain of how and when to introduce peanut. This guideline provides practical, evidence-based advice for stratifying infants with various risk factors for peanut allergy and approaching these different scenarios. D.A.K.

of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel.

Ann Allergy Asthma Immunol. 2017;118:166-173.e7. •

Anaphylaxis

Since the last practice parameter update in 2011, there have been several important findings affecting the clinical management of stinging insect hypersensitivity. This evidence is incorporated into the 2016 practice parameter update.

The update includes 28 summary statements organized into seven sections. Important changes include a discussion of the indication for venom immunotherapy (VIT) in adults with cutaneous systemic reactions: a group at low risk of progression or severe reactions. A new section addresses mast cell disorders and measurement of basal serum tryptase. While VIT is beneficial for patients with mast cell disorders, the failure rate and risk of systemic reactions are higher than average. A new section on venom skin testing addresses the technique of intradermal skin testing and criteria for a positive test result.

A new section on diagnostic testing presents evidence on recombinant/component resolved diagnosis and basophil activation tests. A discussion of the risks of cardiovascular medications in patients with insect allergy addresses recent findings on beta-blockers and angiotensin-converting enzyme inhibitors. New recommendations for identifying groups at high and low risk of anaphylactic reactions are presented. Recommendations for VIT protocol, procedures, and problems address starting doses, updosing regimens, and maintenance doses, along with VIT during pregnancy and adverse reactions. A recommendation on duration of VIT suggests that "5 years is better than 3 years."

The updated practice parameter provides a comprehensive approach to stinging insect hypersensitivity, based on current evidence. Clinicians should be aware that some recommendations differ from those included in the FDAapproved product labeling.

COMMENT: Diagnosis and management of patients with allergic reactions to stinging insects remains solely in the realm of the allergist. Thus staying current on changes to this field is important. This parameter, published in 2017, provides some very significant updates from the 2011 parameter. The most significant change is that the majority of adults who have cutaneous systemic reactions to stings do not require VIT. Additional important updates discuss mast cell disease in sting reactions, risk of beta-blockers and angiotensin enzyme inhibitors during VIT, and safety of rush VIT.

D.A.K.

Golden DBK, Demain J, Freeman T, et al: Stinging insect hypersensitivity: a practice parameter update 2016.

Ann Allergy Asthma Immunol. 2017;118:28-54.

Togias A, Cooper SF, Acebal ML, et al: Addendum guidelines for the prevention

The most recent practice parameter on the diagnosis and management of anaphylaxis was issued in 2010. In 2015, a joint task force of allergy specialty organizations prepared a practice parameter update, based on expert analysis of the available evidence.

The 2015 update includes 73 summary statements organized into nine sections. Recommendations for management of patients with a history of anaphylaxis emphasize the importance of preventive measures, including self-injectable epinephrine and allergen avoidance. Recommendations for office management start with measures to prepare for recognizing and responding to anaphylactic episodes. Subcutaneous immunotherapy injections are the most common cause of anaphylaxis in the allergy office; delayed epinephrine treatment is thought to be the main contributor to fatal reactions.

Recommendations for diagnosis of anaphylaxis to foods are presented; allergen avoidance is "the mainstay of longterm management." A section on drugs and biological agents notes that medications are the main cause of anaphylaxis in adults and of fatal anaphylaxis. Recommendations for insect sting anaphylaxis emphasize the diagnostic importance of clinical history. Other topics include anaphylaxis in the perioperative period, anaphylaxis related to seminal fluid, exercise-induced anaphylaxis, reactions to subcutaneous immunotherapy, and mastocytosis-related anaphylaxis.

The updated practice parameter provides a comprehensive update on evidence-based recommendations for anaphylaxis management. It also presents a section on controversies and unsettled issues, including groups of patients in whom the need for self-injectable epinephrine may be questioned.

COMMENT: This is a divergence from the previous parameter on anaphylaxis, in that four new sections were added. These include a discussion on the definition of anaphylaxis, controversies and unsettled issues related to anaphylaxis, anaphylaxis in mastocytosis and monoclonal mast cell activation syndrome and unusual presentations of anaphylaxis. The authors explore in detail the literature regarding whether autoinjectable epinephrine should be prescribed for patients receiving subcutaneous immunotherapy, who have large local reactions to Hymenoptera, who suffer from oral allergy syndrome; or children who have solely had contact urticaria with food exposure. In each case, the authors demonstrate a lack of consensus and provide a reasonable approach to risk stratifications. Another controversy explored is the use of ACE inhibitors in patients undergoing immunotherapy to Hymenoptera; the authors conclude that this decision must be based upon analysis of the risk-benefit and is best dealt with through a multispecialty approach involving the allergist and cardiologist or nephrologist.

The authors also examine whether a patient presenting with mild systemic symptoms should be treated with antihistamines and/or corticosteroids and with observation versus injectable epinephrine. They conclude that, based on the pharmacodynamic activity of antihistamines or corticosteroids, these agents would not prevent cardiorespiratory arrest or death in many instances. Furthermore, although antihistamines will have effects on histamine, other mediators—such as platelet-activating factor and kinins which are associated with severe reactions—would not be affected.

The authors opine that as the clinical course of anaphylaxis is unpredictable, prompt and early use of epinephrine should be considered even with mild symptoms. Finally, they discuss the concern of prescribing 0.15 mg of epinephrine in children who weigh less than 15 kg. They note that the recommended dose of epinephrine has varied considerably in the literature, concluding that the optimal dosing regimen is unknown.

J.J.O.

Lieberman P, Nicklas RA, Randolph C, et al: Anaphylaxis—a practice parameter update 2015. Ann Allergy Asthma Immunol. 2015;115:341-384.

The mast-cell mediator tryptase could be a useful biomarker of anaphylaxis. Few studies have evaluated its role in diagnosis of anaphylaxis, particularly in children. This study evaluated factors associated with an elevated tryptase level in children with anaphylaxis.

Of 965 children with anaphylaxis seen at a Canadian children's hospital over 4 years, 203 underwent measurement of serum tryptase within 2 hours of onset. Tryptase levels during and after anaphylaxis were analyzed, including factors associated with an elevated reaction tryptase level of 11.4 μ g/L or greater. Post-reaction tryptase levels, 1 to 10 months later, were measured in 68 children.

Thirty-nine children met the definition of an elevated tryptase level, a rate of 19.2%. On adjusted analysis, severe anaphylaxis was the only factor associated with elevated tryptase during the reaction: odds ratio (OR) 8.0. Factors associated with increased tryptase during the reaction were severe reactions and reactions to milk: beta-adjusted OR 7.5 and 4.0, respectively. Tryptase reaction levels above the threshold of 2 ng/mL + 1.2 × (postreaction tryptase level) identified most cases of anaphylaxis, especially if the post-reaction level was measured within 2 months.

Tryptase is not a sensitive biomarker of anaphylaxis in children, particularly in mild to moderate anaphylaxis. However, serum tryptase may help in diagnosing severe pediatric anaphylaxis, particularly to milk. Comparing tryptase levels during and after the reaction may improve sensitivity, regardless of the triggering allergen.

COMMENT: Although no biomarker can accurately confirm the diagnosis of anaphylaxis, the mast-cell mediator tryptase is useful in some situations. The important finding in this article is that even a relatively low (2 ng/mL) serum tryptase elevation obtained within 2 months of the reaction was associated with severe anaphylaxis, especially in children with cow's milk allergy. The take-home message is that it is helpful to compare tryptase levels obtained within 2 hours of acute episodes to another obtained within 2 months.

S.M.F.

De Schryver S, Halbrich M, Clarke A, et al: Tryptase levels in children • • •

presenting with anaphylaxis: temporal trends and associated factors. J Allergy Clin Immunol. 2016;137:1138-1142.

Hypersensitivity Disorders

Biologic agents targeting specific immune cells or mediators have revolutionized the treatment of autoimmune disorders. Since these agents target key components of normal immune responsiveness, they carry the potential for infections and other adverse effects. This article reviews current knowledge of adverse events related to biologic therapies, including their immunologic mechanisms.

Alterations in immune function associated with biologic agents may manifest as immunodeficiency or autoimmunity. Tumor necrosis factor (TNF) inhibitors-the most widely used type of biologic agents-are associated with an increased risk of bacterial infections, particularly pulmonary and soft tissue infections. This and other safety issues seem to be related to the systemic inflammatory burden of the autoimmune disease, as well as comorbidity and other medications. Combinations of biologic agents may further increase infection risk, without improving clinical efficacy.

The article includes an overview of the risk and characteristics of tuberculosis and other intracellular infections associated with biologic agents. Opportunistic viral infections have been reported, although the association of TNF inhibitors with herpes zoster has not been consistently observed.

Autoimmune effects of biologic therapies may range from isolated autoantibodies to organ-specific or systemic autoimmune diseases. The most frequent autoimmune diseases triggered by TNF inhibitors are vasculitis and systemic lupus erythematosus. The appearance of antinuclear antibody or other isolated autoantibodies does not necessarily mean the patient will develop progressive autoimmune disease. Autoimmune diseases associated with biologics may appear different from idiopathic cases.

Paradoxical inflammation refers to the occurrence of inflammatory conditions for which biologic therapies are effectively used, such as psoriatic skin lesions. Recent evidence suggests Th17 cell involvement in patients with psoriasis due to TNF inhibitor therapy.

COMMENT: This excellent review of biologics used in the treatment of autoimmune disorders gives us a better understanding of the risks and benefits associated with these agents. The authors remind us that, as immunologists, we need to be aware of the risk of infection, such as tuberculosis, or the development of secondary autoimmune disease. We should be monitoring our patients treated with biologic agents to ensure prompt recognition of any of these adverse effects.

V.H.-T.

Her M, Kavanaugh A: Alterations in immune function with biologic therapies for autoimmune disease.

Patients with celiac disease (CD) have innate and adaptive immune responses to gluten-containing foods. With increased recognition of "nonceliac gluten sensitivity," healthcare professionals are seeing patients with symptoms attributed to gluten or wheat, which may overlap with CD symptoms. The authors review the epidemiology, pathogenesis, clinical presentation, diagnosis, and management of CD.

The prevalence of CD in Western populations is estimated at 1%, although CD is generally underdiagnosed. More cases are being recognized in non-Western countries, possibly related to the introduction of wheat-based products. While female predominance has been suggested, serologic studies suggest a similar prevalence in men and women. Diarrhea and malabsorption may occur in young children with CD; growth problems occur in children of all ages. The pathogenesis involves predisposing genes in the presence of gluten ingestion, interacting with environmental factors. Most predisposing gene carriers exposed to gluten do not have CD. The possible role of the intestinal microbiome is under investigation.

Patents with CD present with a wide range of intestinal and nonintestinal symptoms. In adults, osteroporosis and anemia are common symptoms. Diagnosis is based on sensitive and specific serologic assays and intestinal biopsy, along with the response to dietary gluten elimination. Gluten-free diet is the mainstay of treatment, and has become popular even among patients without CD. Other treatments are being studied, including intraluminal agents, immunomodulators, and vaccination.

Patients with CD need long-term monitoring for dietary compliance and complications, including the development of other autoimmune diseases. About 5% of cases of CD are refractory to dietary management; unintentional ingestion of small amounts of gluten is the most common reason for persistent symptoms.

COMMENT: With increasing interest in healthy diets, more and more patients are avoiding consumption of gluten. This article is a reminder that "gluten intolerance" has many faces. Celiac disease, however, continues to be underdiagnosed. The importance of strict avoidance of gluten is reviewed, along with persistence of symptoms in patients who are consuming unintentionally. Long term follow-up is essential. We as allergists are in a unique position to help identify patients who may develop autoimmune disease.

Green PHR, Lebwohl B, Greywoode R: Celiac disease. J Allergy Clin Immunol. 2015;135:1099-1106.

Autoinflammatory disease refers to innate immune system disorders with clinical and laboratory findings consistent with both infectious and autoimmune diseases, as well as typical allergic disease features. The authors review current understanding of autoinflammatory diseases, focusing on the role of inflammasomes.

Patients with autoinflammatory diseases have systemic inflammation involving specific tissues, such as the •••

J Allergy Clin Immunol. 2016;137:19-27. 🔍

skin, joints, conjunctiva, and serosal tissues. These are rare disorders with recurrent, intermittent symptoms, posing a diagnostic challenge for physicians and a frustrating problem for patients and families. The authors list five characteristic signs of autoinflammation; the presence of two or more signs suggests an autoinflammatory disease.

Inflammasomes consist of component processes interacting via specific protein domains. These pyrin and caspase activation and recruitment domains (CARD)—also known as "death domains"—result in activation, oligomerization, and formation of filamentous structures. Inflammasome regulation may occur at multiple steps, including transcription, posttranslation, and receptor signaling. Inflammasome activation leads to release of interleukin (IL)-1 β and IL-18, with an inflammatory cascade including further inflammatory cell recruitment.

Diseases involving inflammasome dysregulation are rare, but include the continuum of disorders known as cryopyrinassociated periodic syndromes (CAPS), NLRC4-associated autoinflammatory disease, familial Mediterranean fever, and pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, among others. The authors discuss the various biologic agents targeting IL-1, which are effective treatments for autoinflammatory diseases.

The clinical review emphasizes the importance of recognizing the classic symptom patterns of autoinflammatory diseases, thus enabling appropriate diagnostic tests and early effective treatment. The authors identify a wide range of unanswered questions regarding autoinflammatory diseases and the role of inflammasomes.

COMMENT: While patients with autoinflammatory syndromes do not make up the bread and butter of the average allergist's practice, these disorders can present with symptoms that may lead to referral to us. Many of these disorders can present with urticarial-like rashes, fevers, and arthralgias. Thus as allergists, we need to be able to recognize, diagnose, and in some cases treat and manage these patients. This review helps explain the immunology behind these disorders, the various presentations, and up-to-date biologic therapies. D.A.K.

Hoffman HM, Broderick L: The role of the inflammasome in patients with autoinflammatory diseases. J Allergy Clin Immunol. 2016;138:3-14.

Immunodeficiencies

In infants undergoing cardiac surgery, the thymus is routinely resected because it obstructs surgical access. As more infants undergo early thymectomy, the effects on immune development remain unclear. This study presents 18-year follow-up data on patients who had early thymectomy.

The study included 11 Swedish patients who underwent thymectomy during surgery for congenital heart defects. Surgery was performed between 6 and 148 days of life. Immune parameters were measured in blood samples obtained before surgery, at 18 months, and at 18 years.

Compared to healthy controls, the early thymectomy group had a clear and consistent reduction in T-cell number.

Lymphocyte number, particularly T cells, was reduced even in preoperative blood samples. At 18 years, the early thymectomy group had lower CD45RA+ naive helper T cells but normal CD45RO+ memory helper T cells. A similar pattern was noted for cytotoxic naive versus memory T cells. The thymectomized group had lower numbers of naive CD4+ and CD8+ T cells. They also had a lower total number of Treg cells, with evidence of oligoclonality, near-absent T-cell receptor excision circles (TRECs), and shorter T-cell telomere length.

Infants undergoing thymectomy have "persistent and severe immunologic dysfunction" at 18 years' follow-up. Larger epidemiologic studies are needed to assess the longterm clinical consequences of early thymectomy.

COMMENT: This letter describes the outcome of 11 patients who underwent thymectomy (more than 90% of thymic tissue removed) before age 6 months and were followed up for 18 years. Earlier studies had reported that early thymectomy is associated with T-cell lymphopenia, with decrease in naive T cells and concomitant rise in memory T-cells, but inconsistent findings regarding Treg cells.

This prospective study found a consistent decrease in T cells. At age 18, the number of naive helper T cells was lower, while the memory helper T cells were unaffected. There were similar findings in the cytotoxic T-cells, with CD8+CD45 RA+ (naive T cells) cells being lower, while no such reduction was seen in the memory T-cell number (CD8+CD45RO+). T regulatory cells also demonstrated diminished numbers. The authors also found that the T-cell receptor repertoire was skewed, with signs of oligoclonality (particularly striking for the CD8+ cells). Finally, there was a significant reduction in thymic output, with near-absence of TRECs and a shorter Tcell telomere length resulting in presumed decrease in replicative potential. The takeaway from this study is that early thymectomy results in persistent and severe immunologic dysfunction even 18 years after the procedure. J.J.O.

Gudmundsdottir J, Óskarsdóttir S, Skogberg G, et al: Early thymectomy leads to premature immunologic ageing: an 18-year follow-up. J Allergy Clin Immunol. 2016;138:1439-1443.e10.

The rare primary immunodeficiency disorder chronic granulomatous disease (CGD) is caused by abnormal functioning of phagocytic NADPH oxidase, leading to recurrent lifethreatening infections. There have been few large-scale clinical trials of treatments for infections in patients with GCD. The authors performed a meta-analysis of evidence on the effects of interferon gamma, antifungal drugs, and antibacterial prophylaxis on the incidence of infections in GCD.

Two studies of interferon gamma included 163 patients. The rate of severe infections was 23% in patients receiving interferon gamma versus 54% in the comparison groups, for a relative risk of 0.46. Interferon gamma was associated with an absolute risk reduction of 31%, with a number needed to treat of 3. Pulmonary infections were also significantly reduced.

The analysis of antifungal drugs comprised two studies including 172 patients. Incidence of infections was • • •

6% with antifungal drugs versus 16% without. There was no significant reduction in *Aspergillus* infections. A literature search found no randomized controlled trials of antibacterial prophylaxis in patients with GCD.

Based on two relatively small studies, interferon gamma appears to reduce the risk of severe infections in CGD. Trials of antifungal drugs are inconclusive, while studies of antimicrobial prophylaxis are nonexistent. The authors emphasize the need for large multicenter trials to evaluate treatment to prevent infections in patients with GCD.

COMMENT: This meta-analysis includes limited numbers, but the data show impressive reduction of infection risk in patients with GCD treated with interferon gamma. There are limited data supporting the use of prophylactic antifungals, although there was no significant reduction in *Aspergillus* infections, which are the most common fungal pathogen in GCD. There are no prospective studies supporting the use of antibiotics, although most patients do receive trimethoprim-sulfamethoxazole. The bottom line is that there is evidence from randomized controlled trials supporting the use of interferon- γ prophylaxis in GCD, but not for prophylactic antifungals or antibiotics.

S.M.F.

Loffredo L, Perri L, Zicari A, et al. Chronic granulomatous disease as an SOS call for multicenter cooperative effort to prevent infections.

Ann Allergy Asthma Immunol. 2016;117:285-289.

Patients with primary immunodeficiency (PI) have high rates of severe infections, immune dysregulation leading to autoimmune disease and abnormal inflammatory responses, and malignancies. More than 200 genetic causes of PI have been identified to date. An updated practice parameter for diagnosis and management of PI disorders is presented.

The 2015 update includes a total of 239 evidence-based summary statements. After a series of recommendations addressing general principles of diagnosis and management, the document includes statements relevant to a wide range of PIs: combined B- and T-cell immunodeficiencies, including severe combined immunodeficiency; various well-defined syndromes with immunodeficiency; predominantly antibody deficiencies, including agammaglobulinemia and common variable immune deficiency; diseases of immune dysregulation; phagocytic cell defects; defects of innate immunity; autoinflammatory disorders; complement deficiencies; and anti-cytokine autoantibodies.

The practice parameter also features a series of algorithms outlining the general approach to diagnosis of PI as well as diagnosis of combined or syndromic immunodeficiencies, diseases of immune dysregulation, phagocyte defects, innate immune defects, and autoinflammatory syndromes. Information on the classification of PIs, laboratory findings, and clinical associations is presented as well.

Diagnosis and treatment of PI disorders should be guided by professionals and centers with knowledge and experience in managing these disorders. The authors hope their practice parameter will increase awareness of PIs, enable more consistent evaluation and management, and lead to optimal outcomes for affected patients and families. **COMMENT:** This practice parameter demonstrates our increased understanding of PI diseases. The authors share how to categorize the PI according to the cell type affected in order to best help these patients. We can also appreciate that patients with PI do not only present with recurrent infections. There is an increasing recognition of autoinflammatory diseases and malignancy in our patients with PI, which can aid in diagnosis and treatment. Improved recognition is necessary to improve outcomes for patients with PI.

Bonilla FA, Khan DA, Ballas ZK, et al: Practice parameter for the diagnosis and

management of primary immunodeficiency.

J Allergy Clin Immunol. 2015;136:1186-205.e1-78.

Eosinophilia/Gastrointestinal

Eosinophilic esophagitis (EoE) is increasingly recognized, with an estimated prevalence of 0.4% in Western countries. The authors review the diagnosis, pathophysiology, clinical characteristics, and treatment of EoE.

Eosinophilic esophagitis is a chronic, immune- or antigenmediated disease with symptoms related to esophageal dysfunction and eosinophilic inflammation. Initial symptoms in children include feeding problems, vomiting, and abdominal pain; adolescents and adults may experience dysphagia and food impaction. Esophageal biopsy shows eosinophilia of 15 eosinophils/hpf or greater. Exclusion of gastroesophageal reflux disease is essential, but may be difficult to achieve. Several environmental factors predisposing to EoE have been identified, with evidence of a genetic component. The development of EoE appears to involve Th2 cell activity, mainly induced by food antigens.

Symptoms of EoE are variable and nonspecific, and may be "accommodated" by patients in subtle ways. Characteristic endoscopic appearances and histologic findings have been identified; barium esophagography may be performed to assess the esophageal lumen. Treatment aims to relieve symptoms, control inflammation, and restore function. Diet therapy, such as the six-food elimination diet, seeks to identify and eliminate the allergenic food. Medical treatment includes proton pump inhibitors and topical oral glucocorticoids. Esophageal dilation may be performed to treat narrowing. The role of long-term maintenance therapy is controversial; in most patients, inflammation and symptoms recur if treatment is stopped.

Awareness, understanding, and appropriate treatment of EoE have increased over the past two decades. Continued research is needed to understand the implications of this chronic disease, develop new therapeutic approaches, and show the safety and efficacy of long-term treatment.

COMMENT: Eosinophilic esophagitis remains a disease about which we wish we knew more. This review focuses on the epidemiology, clinical features, pathophysiologic mechanisms, diagnosis, and treatment approaches for children, adolescents, and adults with EoE. Our treatment strategies currently include empiric dietary avoidance (six- and fourfood elimination), testing-directed dietary avoidance, • • •

proton pump inhibitors, and topical corticosteroids. There is a need for critical appraisal of evidence to direct management of EoE patients, which—as noted by these authors should ideally entail a team approach including a gastroenterologist, nutritionist, and allergist. D.M.L.

Furuta GT, Katzka DA, et al: Eosinophilic esophagitis. N Engl J Med. 2015;373:1640-1648. •

Hypereosinophila syndrome (HES) is most common in adults, but may also occur in infants and children. Only a few small studies have reported on hypereosinophilia and HES in children. The authors compared the causes, clinical and laboratory findings, diagnosis, and treatment of hypereosinophilia in children and adults.

From 1994 through 2012, a total of 291 patients—37 children and 254 adults—were evaluated for unexplained hypereosinophilia at the authors' institution. Median age was 10.5 years in the pediatric group and 48 years in adults; males predominated among children but not adults.

In both groups, helminth infection was the most common cause of secondary hypereosinophilia. Primary immunodeficiency was diagnosed in 2 children and 1 adult. The most common clinical subtype was idiopathic HES, reported in 46% of children and 47% of adults. Other diagnoses including lymphocytic variant HES, myeloid disorders with eosinophilia, and overlaps disorders—occurred with similar frequency in both groups.

Children had more gastrointestinal symptoms, while pulmonary manifestations other than asthma were more common in adults. Most other symptoms were comparable between groups. About 80% of patients were treated with corticosteroids, with similar responses in adults and children. Anti-interleukin-5 therapy was used in 6 children and 26 adults. Outcomes, including deaths and neoplasms, were not significantly different between groups. At the time of the analysis, 88% of children and 83% of adults had ongoing HES.

The retrospective study suggests that most characteristics are similar for pediatric versus adult patients with hypereosinophilia/HES. Treatment, outcomes, and prognosis are also similar between groups. Diagnostic and treatment approaches developed for adults with hypereosinophilia will likely be appropriate for children as well.

COMMENT: Hypereosinophilia most commonly affects adults who are 20 to 50 years old; less is known about this condition in children. This review of cases seen at NIH is the largest series of pediatric cases of hypereosinophilia. The study demonstrates that although there are differences (eg, rates of pulmonary/gastrointestinal involvement), aspects of clinical presentation and manifestations, diagnosis, treatment, and prognosis are quite similar in children compared to adults. Although centripetal bias may affect the generalizability of these findings, the data provide support for the appropriateness of algorithms for diagnosis and treatment to children with hypereosinophilia.

D.M.L.

Williams KW, Ware JA, Abiodun A, et al: Hypereosinophilia in children and adults: a retrospective comparison.

J Allergy Clin Immunol Pract. 2016;4:941-947.

Drug-induced peripheral eosinophilia often raises concerns about possible severe hypersensitivity reactions (HSRs). The frequency and characteristics of peripheral eosinophilia due to antibiotics are unclear. This study evaluated the rate of and risk factors for peripheral blood eosinophilia in outpatients monitored after receiving antibiotic therapy.

The researchers analyzed a prospective cohort of 824 former inpatients receiving continued intravenous antimicrobial treatment after discharge. Sixty percent of patients were men, and the median age was 60 years; median duration of therapy was 61 days. Associations between antibiotic exposure and eosinophilia and HSRs were analyzed, in models including time-varying indicators of antibiotic treatment.

Twenty-five percent of patients developed eosinophilia, with a median peak absolute eosinophil count of 726/mL. Eosinophilia was more likely with vancomycin, penicillin, rifampin, and linezolid. Thirty percent of patients with eosinophilia developed HSRs, including rash in 32 patients, kidney injury in 31, and liver injury in 13. The association with eosinophilia was significant for rash and kidney injury, hazard ratio 4.16 and 2.13, respectively; but not for liver injury. There were seven cases of possible drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, with four of these patients receiving vancomycin.

The study documents drug-induced eosinophilia in onefourth of patients receiving outpatient intravenous antibiotics. While most of these patients will not develop HSRs, eosinophilia is associated with increased risks of rash and kidney injury. The observed 0.8% rate of DRESS syndrome is higher than previously reported. The authors discuss the possible clinical response to early or large drug-induced increases in peripheral eosinophils.

COMMENT: Although any drug can be implicated in the development of hypereosinophilia and HSR, the risk is largest with the use of antimicrobial agents. This study evaluated a prospective cohort of former inpatients receiving intravenous antibiotic therapy as outpatients to determine whether there is an association between eosinophilia and the development of HSR (rash, renal injury, and liver injury as well as DRESS syndrome). The researchers found that drug-induced eosinophilia was common (25%) with parenteral antibiotics. Although most patients with eosinophilia do not develop HSR (30% with eosinophilia), eosinophilia does increase the hazard rate of development of rash and renal injury, with a nonsignificant trend toward eosinophilia-related liver injury. Furthermore, DRESS syndrome was more common than previously described (0.8%), with over half of this group receiving vancomycin. Lastly, development of HSR following eosinophilia onset was more likely with earlier eosinophilia and higher absolute eosinophil count. All patients with druginduced eosinophilia should be counselled regarding their risk of HSR and monitored for rash and increasing creatinine levels.

110

Blumenthal KG, Youngster I, Rabideau DJ, et al: Peripheral blood eosinophilia and hypersensitivity reactions among patients receiving outpatient parenteral antibiotics. J Allergy Clin Immunol. 2015;136:1288-1294.