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FEATURE ARTICLES

Peanut OIT – Is It Safe Enough?

Oral immunotherapy (OIT) is a promising treatment for peanut allergy, but its use is limited by a significant risk of adverse events (AEs). So far, there are limited data on the safety of peanut OIT in children. The authors pooled data from previous studies to identify predictors of AEs in children undergoing OIT for peanut allergy.

The analysis included 104 children from three studies of peanut OIT. The frequency and characteristics of AEs were identified, along baseline variables associated with AE risk. The typical patient was a white male, under age 4, with a history of atopic dermatitis or other allergic diseases.

Eighty percent of children had one or more AEs likely related to OIT: 72% during the buildup phase and 47% during the maintenance phase. Ninety percent of AEs occurred at home. Systemic reactions occurred in about 42% of children and gastrointestinal symptoms in 49%. Eighty-five percent of AEs were considered mild, 15% moderate, and none severe. The dropout rate was 20%, with half of these due to persistent gastrointestinal symptoms.

On adjusted analysis, AE risk was elevated for children with allergic rhinitis, incidence rate ratio (IRR) 2.9; and larger skin test wheal size, IR 1.4 per 5 mm increase. Wheal size also predicted gastrointestinal symptoms, while AR predicted systemic reactions. During OIT, 61% of children were treated for a total of 240 likely related events; antihistamines were used in 59% and epinephrine in 12%.

The results suggest a high rate of AEs in children receiving OIT for peanut allergy. Allergic rhinitis and larger wheal size are risk factors for AEs, including systemic and gastrointestinal reactions. The authors believe that additional safety studies are needed before OIT is implemented into widespread clinical practice.

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- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Journal of Asthma
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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High AE rates and low desensitization rates have limited the use of OIT for peanut allergy. Anti-IgE therapy with omalizumab might facilitate oral desensitization by allowing more rapid and successful escalation of allergen dose.

Thirty-seven children and adolescents with peanut allergy were randomly assigned to omalizumab (29 patients) or placebo (8 patients). After 12 weeks, patients started an initial rapid desensitization protocol, with up to 250 mg of peanut protein the first day and weekly increases up to 2,000 mg. At week 20, omalizumab was stopped and patients continued on a 2,000 mg dose. Twelve weeks later, they underwent an open challenge with 4,000 mg of peanut protein. If tolerated, they continued on the 4,000 mg daily dose.

On initial rapid desensitization, median tolerated dose was 250 mg in patients assigned to omalizumab versus 22.5 mg in the placebo group. Six weeks after stopping study treatment, 79% of patients in the omalizumab group tolerated 2,000 mg of peanut protein, compared to 12% of the placebo group. Six weeks later, 23 patients in the omalizumab group tolerated a 4,000 mg dose versus 1 patient in the placebo group. There was no significant difference in overall reaction rate, despite much higher doses of peanut protein in the omalizumab group.

Omalizumab enables rapid peanut desensitization within as little as 8 weeks of peanut OIT. In most cases, including patients with high peanut-specific IgE levels, desensitization persists after omalizumab treatment is stopped. The authors call for further studies to determine which patients can benefit most from this approach to peanut OIT.

COMMENT: These two articles address the safety of OIT for peanut allergy in children. MacGinnitie et al combined data from three OIT trials and to examine whether baseline characteristics can predict the relatively high risk for AEs during the treatment. Overall there was a 20% dropout rate, with 80% experiencing AEs; 61% required treatment, 12% with epinephrine. Patients with larger skin test reactions and those with respiratory allergies had a higher incidence of AEs. The authors state that OIT for food allergies should not yet be implemented in widespread practice; they recommend allergen avoidance as the current standard of care.

The study by Virkud et al suggests that omalizumab can improve the safety of OIT. This is the first report from a double-blind, placebo-controlled study using omalizumab for pretreatment and during initial updosing of OIT for peanut allergy in children and adolescents. Although the sample was small, the results were impressive: the omalizumab group tolerated ten times the dose of peanut during initial rapid desensitization. Even after stopping omalizumab, 79% of treated patients were able to tolerate 2,000 mg of peanut, compared to 12% (one patient) in the placebo group. The quest for a safe treatment for our patients with life-threatening peanut allergy continues, although we may be getting closer.

S.M.F.

Virkud Y, Burks AW, Steele PH, et al: Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol. 2017;139:882-888.

MacGinnitie AJ, Rachid R, Gragg H, et al: Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol 2017;139:873-881.

Keywords: food allergies, peanut allergy, OIT, omalizumab

Dosing Omalizumab Based on Basophil Activation Tests for Peanut Allergy

Evidence suggests that omalizumab can improve outcomes in patients with food allergies. However, this remains an off-label treatment, with no established dosing. This study evaluated the use of the basophil allergen threshold activation test (CD-sens) to guide omalizumab dosage in patients with peanut allergy.

The study included 23 adolescents with severe peanut allergy including anaphylactic symptoms. All underwent CD-sens measurement before and after 8 weeks of normal-dose omalizumab therapy. Depending on whether the CD-sens was "suppressed," patients either underwent peanut challenge or received another 8 weeks of omalizumab, at an increased dose. At the end of that course, they underwent peanut challenge or received another 8-week cycle of omalizumab.

Fifteen patients required increased-dose omalizumab to suppress CD-sens. This group had a baseline CD-sens value of 1.49, compared to 0.32 in those managed with normal-dose omalizumab. After 8 to 24 weeks of C-sens-guided omalizumab therapy, 18 of 23 patients had no objective allergic symptoms in response to peanut challenge (mean dose 2,352 mg). The remaining 5 patients had only mild symptoms. Patients receiving increased-dose omalizumab group had a higher median Ara h 2 IgE-ab/IgE ratio: 17% versus 11%.

The study finds good outcomes with individually dosed omalizumab therapy, guided by CD-sens, in patients with severe peanut allergy. With further studies to confirm these results, the CD-sens and/or Ara h 2/IgE ratio may make it possible to predict which patients will need increased-dose omalizumab.

COMMENT: Early anti-IgE trials for peanut allergy showed some promise. This study followed basophil activation tests to determine if omalizumab dosing was adequate; if the test was not suppressed enough, the dose of omalizumab was further increased. Twenty-three patients underwent initial peanut challenge followed by normal- or high-dose omalizumab, followed by repeat challenge. Fifteen reached the final peanut challenge dose after omalizumab. Unfortunately, challenges were not performed prior to updosing of omalizumab to see if this higher dosing had an added beneficial clinical effect.

D.A.K.

Brandström J, Vetander M, Lilja G, et al: Individually dose omalizumab: an effective treatment for severe peanut allergy. Clin Exp Allergy. 2017;47:540-550.

Keywords: omalizumab, peanut allergy

Expired Epinephrine Can Still Deliver

Especially since recent price increases, allergy patients are asking whether they can use their EpiPens beyond the marked expiration date. The authors tested the potency of EpiPens at various times after their expiration dates.

The researchers collected and tested 31 unused, expired EpiPens and 9 EpiPen Jrs. The devices were 1 to 50 months past their marked expiration date. Samples from each device were tested for epinephrine concentration using liquid chromatography-tandem mass spectrometry.

None of the tested samples were discolored. The epinephrine content was at least 90% of the stated concentration for 65% of EpiPens and 56% of EpiPen Jrs. All devices contained at least 80% of the labeled concentration.

The results suggest that expired EpiPens still contain substantial concentrations of epinephrine—even up to 4 years after their marked expiration date. The results may help in answering patients' questions about expired EpiPens, and suggest that the process for setting expiration dates should be revisited.

COMMENT: We commonly hear patients inquire whether they can use drugs after the expiration date. Several reports indicate expired drugs still retain their potency beyond the date stipulated on the label. This report should not lead to our recommending anything other than refilling epinephrine in accordance with the expiration date. However, outdated epinephrine could have a salutary effect in an emergency where it's the only alternative available. If confirmed in larger studies, the results would merit reconsideration of expiration dating for epinephrine.

D.M.L.

Cantrell FL, Cantrell P, Wen A: Epinephrine concentrations in EpiPens after the expiration date. Ann Intern Med. 2017;166:918-919.

Keywords: anaphylaxis, epinephrine

The Importance of Endotype in Asthma

There is no standard approach to assessing the variable response to systemic corticosteroids in children with severe asthma. The authors assessed phenotypic and endotypic predictors of response to intramuscular triamcinolone.

The study included 56 children and adolescents with severe asthma treated with intramuscular triamcinolone (1 mg/kg to a maximum of 60 mg) at an outpatient severe allergy clinic. Based on the Asthma Control Questionnaire, 15 children had controlled severe asthma, 24 achieved control after triamcinolone, and 17 did not achieve control with triamcinolone. Baseline phenotypic characteristics were

similar across these three groups. All groups had decreases in blood eosinophils and exhaled nitric oxide decreased after triamcinolone; however, the nonresponders had no improvement in lung function or disease-related quality of life.

In contrast to phenotype, endotypic features were significantly related to triamcinolone response. Systemic mRNA expression of inflammatory cytokines and chemokines involved in the interleukin (IL)-2, IL-10, and tumor necrosis factor (TNF) pathways were strong markers of lack of asthma control after triamcinolone. On more stringent analysis, just four genes differentiated between groups: *AIMP1, CCR2, IL10RB,* and *IL5*.

Among children with severe asthma, the study identifies three patterns of asthma control associated with differing responses to systemic triamcinolone. Inflammatory mediators involved in the IL-2, IL-10, and TNF pathways can identify children who do not achieve control with triamcinolone; phenotypic characteristics are of limited value. The authors call for further molecular studies to identify children who can benefit from systemic corticosteroid step-up therapy for severe asthma.

COMMENT: It has long been known that severe asthma in children is a heterogeneous disorder associated with variable responses to corticosteroid treatment. Unfortunately, indicators of corticosteroid responsiveness in children are lacking. Fitzpatrick and colleagues attempted to characterize predictors of response to intramuscular triamcinolone among children with severe asthma. They identified three groups: controlled severe asthma, children who achieved control after triamcinolone, and those who did not achieve control. Clinical phenotypic predictors were of limited utility in predicting triamcinolone response. However, systemic mRNA expression of inflammatory cytokines and chemokines related to IL-2, IL-10, and TNF signaling pathways strongly differentiated children who failed to achieve control with triamcinolone. This study demonstrates that alternative prediction models including more than clinical phenotypic features—such as molecular endotype—are needed to identify which children are likely to derive the most clinical benefit from systemic corticosteroid step-up therapy.

J.J.O.

Fitzpatrick AM, Stephenson ST, Brown MR, et al: Systemic corticosteroid responses in children with severe asthma: phenotypic and endotypic features. J Allergy Clin Immunol Pract. 2017;5:410–419.e4.

Keywords: asthma (child), asthma (severe), endotypes, phenotypes

Sleep Apnea: Another Potential Cause in Uncontrolled Asthma

Some studies have reported improvements in asthma-related outcomes with continuous positive airway pressure (CPAP) in asthmatic patients with comorbid obstructive sleep apnea (OSA). This prospective study evaluated the medium-term effects of CPAP on asthma outcomes in a large sample of patients with asthma and OSA.

The study included 99 adult patients with asthma and OSA treated at 15 Spanish hospitals. The patients, mean age 57 years, had moderate to severe OSA: respiratory disturbance index score 20 or higher. Clinical and functional asthma outcomes were evaluated after 3 and 6 months of CPAP.

Mean Asthma Control Questionnaire score decreased from 1.39 at baseline to 1.0 after 6 months of CPAP. The percentage of patients with uncontrolled asthma decreased from 41.4% to 17.2%. The percentage with asthma attacks decreased from 35.4% to 17.2%.

Asthma-related quality of life improved significantly among patients with severe asthma or OSA. Other benefits of CPAP included reduction in gastroesophageal reflux and rhinitis symptoms and improvement in bronchial reversibility and exhaled nitric oxide. There was no change in asthma medications or patients' body weight during asthma treatment.

This multicenter trial supports the benefits of CPAP for asthmatic patients with moderate to severe OSA. Six months of CPAP are associated with improvements in current and future asthma control. The effects are larger in patients with more severe asthma or OSA, those with uncontrolled asthma, and those with better CPAP compliance.

COMMENT: Several pilot studies have demonstrated that CPAP improves asthma control in asthma patients with OSA. This study attempts better methodologic evaluation of this intervention. The addition of CPAP therapy improved not only asthma control and quality of life, but also future risk. Furthermore, the affect was more significant in patients with more severe asthma or OSA. The study further supports the need to screen for and treat OSA in patients with severe or poorly controlled asthma.

J.J.O.

Serrano-Pariente J, Plaza V, Soriano JB, et al: Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea. Allergy. 2017;802-812.

Keywords: asthma (adult), obstructive sleep apnea

Shared Decision-Making May Help Adherence to Asthma Plans

There is a growing emphasis on shared decision-making approaches in patients with chronic diseases, particularly when there are multiple treatment options. Shared decision-making might be a useful approach to addressing the problem of nonadherence with recommended asthma treatments. The authors discuss the potential for shared decision-making to improve treatment adherence in adult asthma patients.

The concept of shared decision-making is well-accepted by patients, clinicians, and other stakeholders. • • •

However, there are obstacles and challenges to implementing this approach into everyday clinical care for adult asthma. For success in shared decision-making, patients must understand the role that their preferences play in the decision process. They must be able "to provide their own expertise in the form of values and preferences," and understand why the treatment plan should reflect their preferences. Physicians can use objective measures of asthma-related outcomes as a complement to patient values and preferences.

The authors outline a framework of the factors affecting patients' willingness and ability to adhere to asthma controller medications. Even for motivated patients, patient-related and structural barriers such as cost, side effects, or lack of access to physicians may negatively affect adherence. In addition to directly increasing patients' knowledge, shared decision-making may work indirectly by appealing to social, cultural, and behavioral characteristics.

Some studies have described the association between shared decision-making and adherence in asthma and other chronic diseases. But despite promising clinical trials, there has been little progress toward implementing this approach into routine clinical care. Further studies are needed not only to demonstrate the efficacy of shared decision-making, but also to gain insights into the major challenges to its effectiveness.

COMMENT: In this position paper, Pollard and colleagues examine the literature regarding shared decision-making—specifically in adults with asthma. It is well-known that adherence with asthma medications is poor overall, and this translates to reduced asthma control, increased symptoms and healthcare expenditures, and reduced quality of life. The authors reinforce that ignoring a patient's personal goal and preferences can translate to reduced adherence. They delineate how a shared approach to treatment decision-making for asthma can be an effective tool for improved adherence.

J.J.O.

Pollard S, Bansback N, FitzGerld JM, Bryan S: The burden of nonadherence among adults with asthma: a role for shared decision-making. Allergy. 2017;72:705-712.

Keywords: action plan, adherence, asthma (adult)

Can AIT Prevent Future Sensitizations?

Allergen immunotherapy (AIT) is the only disease-modifying treatment for allergic rhinoconjunctivitis and asthma. Among the claimed benefits is reduction in the risk of new-onset allergic sensitizations—however, this is based on a small number of observational studies. The authors performed a systematic review of the evidence on risk of new sensitizations after AIT.

A review of the literature identified 18 studies of AIT, with long-term follow-up including assessments of new allergic sensitizations. Eleven studies enrolled children and seven enrolled adults. The studies included a total of 11,106 patients, more than three-fourths from a single study. There was one randomized trial; the rest were observational studies.

The studies were highly heterogeneous in patient population, AIT dosage, and other characteristics. All studies but one were considered at high risk of bias. Ten studies reported a lower risk of new-onset sensitizations after AIT, compared to placebo. However, the strength of evidence supporting this conclusion was rated low.

The analysis questions the strength of evidence supporting AIT's efficacy in reducing the risk of future allergic sensitization. Randomized trials with long-term follow-up, including data on monosensitized children or adolescents, is needed to provide more reliable estimates of this treatment effect.

COMMENT: We frequently advise our patients that in contrast to medications, AIT has the potential to affect the underlying immunologic machinery that drives symptoms. Do the long-term benefits of AIT include reducing future aeroallergen sensitizations? This is the first critical appraisal of the evidence, using the GRADE approach, to support this contention. Study results were inconsistent, and virtually all studies had a serious risk of bias. Because of extreme heterogeneity among these studies, meta-analysis could not be performed. The strength of evidence for supporting an effect of AIT for reducing future sensitizations was low—implying that the confidence with which we discuss this potential benefit with our patients should be modified accordingly.

D.M.L.

Di Bona D, Plaia A, Leto-Barone MS, et al: Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. Allergy. 2017;72:691-704.

Keywords: allergen immunotherapy, allergic sensitization

Allergic Rhinitis in Kids: "Not Just Another Snotty Nose"

Allergic rhinitis (AR) in children and young adults is associated with a very high rate of sleep disturbance. There is currently no quick assessment that captures the quality of life (QOL) impact of sleep disturbance in this group of patients. This study used the National Institutes of Health's Patient Reported Outcome Measurement Information System (PROMIS) to identify the best method of assessing sleep and its health-related QOL impact in young patients with AR.

The study included 144 patients, aged 8 to 30, with AR. Based on the Allergic Rhinitis and Its Impact on Asthma (ARIA) questionnaire, 100 patients had moderate to severe AR. Responses to a single ARIA question suggested that 43% of children and 66% of adults had sleep disturbance. Many patients reported excessive daytime sleepiness, including 37.5% of those who did not report sleep disturbance.

Responses to PROMIS assessments indicated that patients with moderate to severe AR had more sleep disturbance, along with increased anxiety, depression, and fatigue. They also had more trouble with social interactions and perceived more cognitive difficulties. In children under 12, reports of sleep-related impairment were correlated with depression and fatigue but reports of sleep disturbance were not.

A single question is inadequate to screen for sleep disturbance or impairment in young patients with AR. Especially in children, sleep disturbance can influence many aspects of life, including social relationships and daytime functioning. The authors discuss the implications for assessing sleep and other aspects of QOL in patients with AR.

COMMENT: As allergists, we know that being the "booger boy" during springtime is not unusual for some children with pollen allergy. In this survey of pediatric patients with allergic rhinitis, the PROMIS was beneficial in identifying quality of life measures. The authors remind us that a single question about sleep is not enough to truly assess how AR is affecting quality of life. Since sleep disturbance in children can affect daytime functioning and peer relationships, this tool may be useful in identifying the effects of AR in pediatric patients. Larger studies are needed.

V.H.-T.

Dass K, Petrusan AJ, Beaumont J, et al: Assessment of sleep disturbance in children with allergic rhinitis.
Ann Allergy Asthma Immunol. 2017;118:505-506.

Infection Risk with SCIT: Reassuring Results

In response to concern over the risk of serious infections due to contaminated compounded injectable medications, the US Food and Drug Administration has proposed more rigid guidelines for allergen extract preparation and storage. This would make it difficult for allergists to prepare subcutaneous immunotherapy (SCIT) injections in the office. Data from an ongoing surveillance project were used to analyze the risk of infections due to SCIT injections.

The study used 2014-15 data from the web-based surveillance program of the ACAAI and AAAAI, including data from 1,046 SCIT prescribers from 494 North American practices. Respondents were asked about local cutaneous or systemic infections related to mixed allergen vials prepared in the office. In nearly 9.5 million injection visits by 1.4 million patients, no infection events requiring antibiotic treatment were reported. The results provide "no scientific evidence that confirms a risk of infection from SCIT as currently practiced," the researchers write.

COMMENT: Concern about infection following injectable medications may lead to further regulations regarding preparation of allergen immunotherapy. The authors report data from the web-surveillance program among ACAAI and AAAAI members. In more than 1 million patients, and almost 9.5 million injections, no local or systemic infections requiring antibiotics were reported. This reassures us that immunotherapy vaccines currently prepared by allergists do not increase the risk of infection in our patients.

V.H.-T.

Epstein TG, Liss GM, Murphy-Berendts K, et al: Evaluation of the risk of infection associated with subcutaneous allergen immunotherapy: American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology National Surveillance Study on Allergen Immunotherapy, 2014-2015.
Ann Allergy Asthma Immunol. 2017;118:511-512.

Keywords: infection, SCIT

Finally–Another Marker for Severity of Anaphylaxis to Food!

Lower levels of platelet-activating factor acetylhydrolase (PAF-AH) have been linked to an increased risk of life-threatening anaphylaxis. A recent study in children with peanut allergy found that apolipoprotein B-100 is strongly related to PAF-AH activity. The present study assessed serum ApoB as a potential biomarker of the severity of anaphylactic reactions to foods.

The study included 837 children referred for evaluation of clinically suspected food allergy. Serum ApoB was analyzed for association with the severity of each child's most severe accidental reaction, scored according to the organ systems involved.

The severity of food reactions was inversely related to ApoB concentration, independent of patient and clinical characteristics. On subgroup analysis, the association was significant for children with a positive history but negative food challenge, but not those with a positive history and challenge. Apolipoprotein B-100 level was not associated with the outcome or severity of reaction to food challenge.

Serum ApoB may be a biomarker of the severity of anaphylactic reactions in children with suspected food allergy. The authors discuss the potential use of this biomarker, including the possible reasons for the association in children with negative food challenges.

COMMENT: Deficiency of PAF-AH has been shown to lead to increased risk of life-threatening anaphylaxis. This study investigated levels of ApoB, which makes up low-density lipoprotein molecules to which PAF-AH circulates in complexes. Severity of accidental reaction by history was inversely associated with the concentration of ApoB, as seen in patients with a positive history and negative food challenge. The authors note that ApoB can be measured from stored frozen serum and is more convenient. This is an area that should be studied further in patients with other types of anaphylaxis.

V.H.-T.

Pettersson ME, Koppelman GH, Flokstra-de Blok, et al: Apolipoprotein B: a possible new biomarker for anaphylaxis.
Ann Allergy Asthma Immunol. 2017;118:515-516.

Keywords: anaphylaxis, biomarkers, food allergy

The Burden of Chronic Urticaria: 'It's Worse Than We Thought'

Most studies of chronic spontaneous urticaria (CSU) have reported on highly selected groups of patients treated in specialty care. The authors present initial results from a worldwide study of chronic urticaria in real-world settings.

The authors present data on the first 1,539 German patients enrolled in the prospective AWARE study ("A Worldwide Antihistamine-Refractory chronic urticaria patient Evaluation"). All had H1-antihistamine-refractory CSU diagnosed more than 2 months previously. Demographic characteristics, disease activity, and patient-reported outcomes were assessed.

Seventy percent of patients were women. The mean age was 46 years, with a peak prevalence between 45 and 55 years. Mean time since CSU diagnosis was 4.8 years. Mean Urticaria Control Score was 7.9; more than three-fourths of patients had a score of less than 12, indicating uncontrolled urticaria. About half of patients had angioedema. Common comorbid conditions included chronic inducible urticaria, allergic rhinitis, hypertension, asthma, and depression.

About 58% of patients were taking one or more medications: most commonly second-generation H1-antihistamines, followed by first-generation H1-antihistamines and corticosteroids. Patients reported "marked impairment" in quality of life, with 62% reporting a moderate or larger impact. About 30% reported using emergency services: average 3 visits. The same proportion reported hospitalization, average 2.3 times.

The results suggest that H1-antihistamine-refractory CSU has a major impact on the lives of affected patients in routine clinical care. Most patients appear to be undertreated, with high rates of uncontrolled urticaria and large effects on quality of life. The findings highlight the need for improved patient care and adherence to treatment guidelines for CSU.

COMMENT: This study evaluated more than 1,500 German patients with antihistamine-refractory urticaria in regard to burden of disease, treatment, and healthcare utilization. Over 40% of patients had angioedema in the past 6 months and 21% had associated physical urticaria. In approximately one-third of patients, CSU resulted in a very large or extremely large impact on quality of life; a similar proportion went to the ED or were hospitalized for CSU. Nevertheless, only 58% of patients were receiving any treatment—suggesting that most patients are undertreated for this burdensome disease.
D.A.K.

Maurer M, Staubach P, Raap U, et al: H1-antihistamine-refractory chronic spontaneous urticaria: it's worse than we thought – first results of the multicenter real-life AWARE study. Clin Exp Allergy. 2017;47:684-692.

Keywords: chronic spontaneous urticaria, disease burden

Pre-eclampsia and Allergy - It All Begins Before Your First Breath

Pre-eclampsia is a pregnancy complication associated with excessive maternal inflammation, related to disturbance of the immune tolerance between mother and fetus. Inflammation during pregnancy may contribute to childhood allergic disease risk. Population-based data were used to analyze the association between pre-eclampsia and risk of asthma, allergy, and eczema in offspring.

The study included a high-risk birth cohort of 411 children enrolled in the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$). Of these, 5.6% were born to mothers diagnosed with pre-eclampsia. Pre-eclampsia was analyzed for association with asthma, allergy, and eczema, diagnosed prospectively; and lung function, measured at 1 month and 7 years of age. Associations between pre-eclampsia and childhood allergy were also analyzed using Danish national registry data.

Maternal pre-eclampsia was associated with an increased rate of treatment with inhaled corticosteroid at age 7, adjusted odds ratio (OR) 4.01; increased risk of allergic rhinitis, OR 4.83; and increased bronchial responsiveness to methacholine, adjusted β-coefficient log-μmol -0.80. Children born to mothers with pre-eclampsia also had higher rates of aeroallergen and food sensitization and higher total IgE levels.

In the national registry data, 3.7% of children were born after pregnancies associated with pre-eclampsia. These offspring had elevated rates of asthma, eczema, and aeroallergen and food sensitization, particularly if pre-eclampsia lasted 2 weeks or longer. Mothers with a history of asthma were more likely to developed pre-eclampsia.

Maternal pre-eclampsia appears to increase the risk of childhood asthma, eczema, and allergy. The results add to evidence that pregnancy is a critical period for immune programming in offspring, and that exposure to inflammation in utero may lead to persisting immune deregulation.

COMMENT: The fetal insult seen with pre-eclampsia, during a critical developmental period, causes significant downstream effects. Although postnatal events may act as a modifying factor, the duration of pre-eclampsia is a significant contributor. This observation from the landmark COPSAC$_{2000}$ cohort allows further insight to the determinants of childhood asthma, allergy, and eczema. (Also see the accompanying editorial: Am J Respir Crit Care Med. 2017;195:546-548.)
B.E.C.

Stokholm J, Sevelsted A, Anderson UD, Bistar H: Preeclampsia associates with asthma, allergy, and eczema in childhood.
Am J Respir Crit Care Med 2017;195:614-621.

Keywords: asthma (child), pre-eclampsia, risk factors

Can Periostin Help Predict Asthma in Children?

It would be of value to have noninvasive biomarkers to predict which children with early-life wheezing will go on to develop asthma. Periostin is a marker of type 2 airway inflammation in adults; there is little information on periostin levels in early life. The authors evaluated periostin, blood eosinophils, and allergic sensitization as predictors of childhood asthma.

The study used data on 289 infants at high risk for asthma and allergic disease, drawn from the COAST (Childhood Origins of ASThma) study. Serum-specific IgE, eosinophil count, and periostin were measured in blood samples obtained at age 2, 4, 6, and 11 years from 244 children. These biomarkers were evaluated as predictors of clinical asthma at age 6 and 11.

Serum periostin was highest at age 2, geometric mean 145 ng/mL, with no significant change in later years. The measured levels were two to three times higher than previously reported in adults. Children who had a periostin level of 150 ng/mL or higher at age 2 had a twofold increase in the risk of asthma at age 6: odds ratio (OR) 2.3.

Risk was about three times higher for children with an eosinophil count of 300 cells/μL or higher or aeroallergen sensitization at age 2: OR 3.1 and 3.3, respectively. For children with two or more risk factors, the OR for childhood asthma increased to 6.6.

Serum periostin, blood eosinophil count, and aeroallergen sensitization all predict an increased risk of childhood asthma. High periostin levels in early childhood, reflecting bone turnover, limit its value as a clinical predictor. Risk of childhood asthma is highest for young children with evidence of multiple pathways of type 2 inflammation.

COMMENT: The potential to predict which children with wheezing will develop asthma could be helpful in targeting therapy in the new "personalized medicine" paradigm. Using data from the prospective COAST birth cohort study, this report evaluated three potential biomarkers, including periostin, at ages 2, 4, 6 and 11 years to predict development of asthma. Since periostin is also elevated during bone growth, it is not surprising that periostin levels are about three times higher in children than adults. Therefore periostin had only modest value as a predictive marker for allergic asthma in children. The authors conclude that combining two or more biomarkers as early as 2 years can provide additional predictive value.

S.M.F.

Anderson HM, Lemanske Jr, RF, Arron JR, et al: Relationship among aeroallergen sensitization, peripheral blood eosinophils, and periostin in pediatric asthma development. J Allergy Clin Immunol. 2017;139:790-796.

Keywords: asthma (child), biomarkers, periostin

Type of Fat Impacts Childhood Asthma

Most attempts to explain the mechanism of the association between obesity and asthma rely on body mass index (BMI) as a marker of body fat and body composition. This overlooks the possible role of fat mass distribution, which is associated with other health risks. The authors evaluated the contribution of fat mass distribution to risk of childhood asthma.

The analysis included data on 6,178 children, aged 6 years, enrolled in a Dutch prospective cohort study. Body fat distribution was measured by dual-energy x-ray absorptiometry. Total body and abdominal fat were evaluated for association with respiratory resistance (Rint), exhaled nitric oxide, and risk of childhood wheezing and asthma.

Children with higher BMI had a higher Rint, Z score 0.06; and increased risk of wheezing, odds ratio 1.07 per Z score increase in BMI. Body mass index was unrelated to exhaled NO or childhood asthma.

Significant associations were noted for measures of body fat distribution, including a positive association between fat mass index and Rint: Z score 0.40. Exhaled NO was lower for children with a high android/gynoid fat mass ratio, Sym% 9.8; but higher for those with a high preperitoneal fat mass, Sym% 6.5. Subcutaneous fat mass, measured by ultrasound, was unrelated to childhood wheezing or asthma.

The results suggest that detailed information on body fat distribution may help to clarify the association between obesity and childhood wheezing and asthma. Changes in airway function and inflammation may be related to visceral fat rather than general adiposity. Further studies are needed to confirm these observations and clarify the direction of the associations.

COMMENT: These Dutch researchers measured a variety of fat indices, exhaled NO, and Rint in a large cohort of children at age 6 to characterize the obese-asthma phenotype. The interesting findings are that there was variation in the location of body fat and asthma markers. In general, visceral fat—particularly preperitoneal fat mass—was associated with higher exhaled NO and lower Rint, whereas higher BMI was associated with higher Rint and wheezing symptoms. The authors suggest that inflammatory adipokines, such as leptin, may contribute to airway inflammation in these children and that BMI may not be the best measure to predict obese-asthma.

S.M.F.

den Dekker HT, Ros KPI, de Jongste JC, et al: Body fat mass distribution and interrupter resistance, fractional exhaled nitric oxide, and asthma at school-age.
J Allergy Clin Immunol. 2017;139:810-818.

Keywords: asthma (child), obesity

AERD: A Scoring System for Adjudicating Reactions

Many patients with asthma, especially severe asthma, have aspirin-associated respiratory disease (AERD). This diagnosis is confirmed by provocation challenge resulting in upper and/or lower airway reactions. Current approaches to test interpretation are based on clinical judgment. The authors report a quantitative scoring system for interpreting the results of provocation challenge for suspected AERD.

The study included 115 patients undergoing provocation challenge using intranasal ketorolac with modified oral aspirin. Patients were asked to rate ten symptoms typically experienced during provocation challenge, on a 10-point scale from mild to severe. The scores were added to provide a composite symptom score at baseline, at 30-minute intervals following ketorolac challenge, and at 60- and 90-minute intervals during aspirin challenge.

One hundred patients were classified as aspirin or NSAID reactors. Composite symptom score at the time of reaction was 15.3 in reactors, compared to a highest score of 7.8 in nonreactors. Nearly 70% of reactors had at least a 5-point increase in symptom score, compared to none of the nonreactors. Only about half of patients would have been classified as reactors based on objective measures (nasal inspiratory flow and FEV_1) only.

The ten-symptom composite score provides a simple and quantifiable measure of response to provocation challenge testing for AERD. An increase of 5 points or more is "moderately sensitive and highly specific" for identifying reactors to aspirin or NSAID challenge.

COMMENT: With inclusion of intranasal ketorolac in the first stage of aspirin challenge, this procedure is associated with fewer serious respiratory reactions, such that the majority of AERD patients exhibit isolated upper airway reactions. Objective measures (FEV_1 or peak nasal inspiratory flow rates) lack sufficient sensitivity for optimal identification of reactors. For this reason, adjudication of a positive challenge is frequently subjective. This retrospective analysis demonstrates the utility of a quantitative scoring system that, in the absence of a valid biomarker for AERD, can serve as a valuable aid for confirming a positive reaction during intranasal ketorolac and oral aspirin challenge/desensitization.

D.M.L.

Cook KA, Modena BD, Wineinger NE, et al: Use of a composite symptom score during challenge in patients with suspected aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2017;118:597-602.

Keywords: AERD, diagnosis

After Removal of Pholcodine, Tolerance of NMBAs Increases

Pholcodine, which induces IgE antibodies to substituted ammonium ion epitopes might explain anaphylactic reactions of neuromuscular blocking agents (NMBAs) in previously unexposed patients. In Norway, reductions in IgE sensitization and anaphylaxis to NMBAs were reported 3 years after removal of a pholcodine-containing cough medicine. The current study extends follow-up to 6 years after withdrawal of pholcodine.

The researchers analyzed 650 acute reports to the Norwegian Network for Anaphylaxis under Anaesthesia between 2005 and 2013. The pholcodine-containing cough medicine was withdrawn in 2007. During 2008-10 and 2011-13, there were significant reductions in total acute reports, as well as reports with IgE antibodies to pholcodine and succinylcholine. Total NMBA sales at 6 years' follow-up were 83% the value at baseline. Throughout the period studied, succinylcholine and rocuronium accounted for 86% of sales.

Five patients died from NMBA-related anaphylaxis during the baseline and initial 3-year follow-up periods, compared to none in the 6-year follow-up period. By 4 to 5 years' follow-up, the prevalence of IgE sensitization to succinylcholine in patients with suspected allergy decreased to zero.

The results show continued reduction in IgE sensitization and clinical reactions to NMBAs in Norway since elimination of pholcodine. Exposure to pholcodine-containing cough medicine may be associated with a "considerable number' of fatal anaphylactic reactions in other countries.

COMMENT: Pholcodine, an opioid-based cough suppressant structurally similar to succinylcholine, was removed from antitussives in Norway in 2007. Since then, the Norwegian population has exhibited a lower prevalence of IgE sensitization to succinylcholine and has become more tolerant of NMBAs. Of 7 fatal cases of intraoperative anaphylaxis reported in a Norwegian registry, 5 were related to NMBAs—none occurred after 2009. In contrast to European studies reporting NMBAs as the most frequent cause of intraoperative anaphylaxis, recent US studies implicate antibiotics (mainly cefazolin) as the most frequent identifiable cause. A possible explanation for this disparity is that populations in selected European countries were sensitized via exposure to cosmetics or other agents with allergenic epitopes that can cross-react with NMBAs. This study provides support for the suggestion that pholcodine serves as such a sensitizer.

D.M.L.

de Pater GH, Florvaag E, Johansson SGO, et al: Six years without pholcodine; Norwegians are significantly less IgE-sensitized and clinically more tolerant to neuromuscular blocking agents. Allergy. 2017;139:813-819.

Keywords: anaphylaxis, intraoperative reactions, NMBAs

Getting a Better Understanding of NERD

The clinical course of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NERD) is variable, as is its management. This study used cluster analysis to identify phenotypic subgroups of patients with NERD.

The study included 302 adults with NERD, treated at a South Korean university hospital between 1996 and 2013. Cluster analysis was performed to identify phenotypes of NERD based on clinical features, inflammatory cells, metabolomic profiles, anti-asthma medication use, and asthma exacerbation rate.

Four NERD phenotypes were identified: subtype 1, NERD with chronic rhinosinusitis (CRS)/urticaria (subtype 1, 83 patients); subtype 2, NERD with CRS but no urticaria/atopy (84 patients); subtype 3, NERD without CRS/urticaria (73 patients); and subtype 4, NERD with urticaria (62 patients). There were significant differences in proportion of females, baseline FEV_1, total IgE level, and peripheral serum and sputum eosinophil counts.

Subtype 1 was associated with more asthma exacerbations than subtype 3. Use of anti-asthma medications, including medium- to high-dose corticosteroids and long-acting β_2-agonists varied among groups. Across NERD phenotypes, serum leukotriene E4 (LTE4) was higher than in patients with aspirin-tolerant asthma. Urine LTE4 was higher in NERD subtypes 1 and 3 versus subtype 2.

The four identified NERD phenotypes differ in their clinical, cellular, and biochemical characteristics. The subtypes also vary in terms of asthma severity and exacerbation risk. Management strategies based on phenotype might improve outcomes for patients with NERD.

COMMENT: Previous investigations using cluster analysis in adult asthmatics have reported distinct subtypes of asthma. These studies reinforce that asthma is a heterogeneous disease and that a stratified approach is needed for each subtype. Using cluster analysis, Lee and colleagues were able to find four distinct subtypes with different clinical/biochemical findings and asthma exacerbations in a cohort of patients with NERD. The authors suggest that strategies relying on subtype classification may help achieve better outcomes in the management of NERD.

J.J.O.

Lee HY, Ye YM, Kim SH, et al: Identification of phenotypic clusters of nonsteroidal anti-inflammatory drugs exacerbated respiratory disease.
Allergy. 2017;72:616-626.

Keywords: AERD, NERD, phenotypes

Crocodiles and Chicken are "Allergy Cousins"

Allergy to chicken meat is considered rare; cross-reactivity with other types of poultry have been reported. A patient with chicken meat allergy who had severe anaphylaxis after ingesting crocodile meat is reported.

The patient was a 13-year-old male who had an anaphylactic reaction after tasting crocodile meat for the first time. He was diagnosed with allergy to chicken meat at age 5, and had experienced several anaphylactic reactions caused by accidental consumption of chicken or turkey. The reaction occurred after his first bite of crocodile meat, including difficulty breathing. He had only a short emergency department stay after home treatment with intramuscular adrenaline and inhaled β_2-agonist. After extensive evaluation, parvalbumin was identified as the common allergen between chicken and crocodile. The 14 kDa crocodile parvalbumin was 94% identical to its chicken homolog.

Patients allergic to chicken meat may be at risk of reacting on their first exposure to crocodile meat. Such unsuspected cross-reactions may become more frequent as "exotic" foods become increasingly available.

COMMENT: This fascinating case report describes a young teenager who experienced anaphylaxis to crocodile meat after first-time ingestion. He had a documented history of reacting to chicken and poultry meat. Extensive testing revealed α-parvalbumin as the main cross-reactive allergen between crocodile and chicken meat.

C.D.

Ballardini N, Nopp A, Hamsten C, et al: Anaphylactic reactions to novel foods: case report of a child with severe crocodile meat allergy.
Pediatrics. 2017;139:e20161404.

Keywords: cross-reactivity, food allergy

To Step Down or Not Step Down? That Is the Question

For patients who have achieved asthma control, the goal of step-down therapy is to reduce medication use without increasing exacerbation risk. This study assessed the roles of adherence, biologic factors, and psychologic factors as predictors of failure in stepping-down asthma therapy.

The study included 222 adults with asthma that was well-controlled on inhaled corticosteroids, with or without long-acting β_2 agonists. The investigators defined three potential risk factors for failure to maintain good asthma control for over one year after step-down. These were Factor B (biologic), chronic upper airway complications; Factor P, psychiatric complications such as sleep, mood, or somatoform disorder; and Factor A, medication adherence of 75% or less.

The indication for step-down therapy was considered appropriate for about 60% of patients. Of those who initiated step-down, 76% maintained disease control. On logistic regression analysis, risk of treatment failure was 23 times higher with Factor A and 11 times higher with Factor B. Risk of failure was greatly increased by combinations of factors: by 21 times with Factors P and A, 24 times with Factors B and A, and 36 times with all three factors.

The study shows the importance and relative strength of adherence, biologic factors, and psychiatric factors as predictors of failure of step-down therapy for asthma. Considering these factors, alone and in combination, may enable a more proactive and targeted approach to step-down therapy.

COMMENT: This fascinating study explored the impact of biologic factors (upper airway disease), adherence, and psychologic issues on the ability to successfully step-down asthma therapy and maintain control. Poor treatment adherence increased the risk of failure in step-down most significantly by 23-fold, and biologic factors increased it by 11-fold. The combination of these two factors increased failure by 24-fold, while psychologic factors plus poor adherence increased failure by 21-fold. All three factors in combination increased the risk by 36-fold. Interestingly, psychologic factors only interacted with the other factors to reduce the chances for stepping-down but were not a problem factor when present alone.

J.J.O.

Saito N, Kamata A, Itoga M, et al: Assessment of biological, psychological and adherence factors in the prediction of step-down treatment for patients with well-controlled asthma. Clin Exp Allergy. 2017;47:467-478.

Keywords: adherence, asthma (adult), psychological factors, step-down therapy

New Insights into Adult Bronchiectasis

In the absence of cystic fibrosis (CF), bronchiectasis in adults is a heterogeneous disorder with varying causes. Despite its high morbidity and associated costs, there are limited data on the characteristics of adult non-CF bronchiectasis (NCFB). The authors present initial data from the US Bronchiectasis Research Registry.

The report includes data on 1,826 adults with NCFB contributed by 13 US centers between 2008 and 2014. Women accounted for 79% of patients, and 77% were between age 50 and 79. Sixty-three percent of patients had coexistent nontuberculous mycobacteria (NTM). Patients with NTM were older, predominantly female, and more likely to have gastroesophageal reflux disease. Those without NTM were more likely to have asthma, primary immunodeficiency, and primary ciliary dyskinesia.

Airflow obstruction was present in 51% of patients; those with NTM were more likely to have diffuse airway dilation and tree-in-bud abnormalities. Patients with NTM were less likely to have *Psuedomonas* and *Staphylococcus aureus* isolated on culture. Patients with NTM were more likely to receive bronchial hygiene measures. Overall, 39% of patients received suppressive antibiotics. Those without NTM received more antibiotics for exacerbations, rotating oral antibiotics, steroids, and inhaled bronchodilators.

This study describes the largest reported cohort of US adults with bronchiectasis. Despite their phenotypic similarities, the data show some significant differences based on the presence or absence of NTM. The authors note the potential for bias, including more patients with NTM, in this tertiary referral cohort.

COMMENT: This study from a US registry on non-CF adult bronchiectasis has several interesting findings. Most patients developed bronchiectasis between 50 and 79 years of age; 79% were women. The most common cause was NTM, but this may be due to referral bias. Asthma was present in 29% of patients while only 5% had a diagnosed primary immunodeficiency. About 40% of patients were treated with antibiotics for acute exacerbations but 39% also received suppressive antibiotics. Several differences were noted between patients with and without NTM.

D.A.K.

Aksamit TR, O'Donnell AE, Barker A, et al: Adult patients with bronchiectasis: a first look at the from the US Bronchiectasis Research Registry. Chest. 2017;151:982-992.

Keywords: bronchiectasis, nontuberculous mycobacteria

Are We Interpreting Bronchodilator Responses Correctly?

There is a lack of consensus on how to interpret tests of bronchodilator responsiveness (BDR) in patients undergoing diagnostic spirometry. The authors assessed the interpretation of BDR in a very large sample of patients undergoing spirometry.

The analysis included worldwide data on 31,528 patients undergoing BDR testing. Baseline FEV_1 had no effect on milliliter changes in FEV_1 and FVC, which were affected by patient age, height, and sex and level of airway obstruction. Among 1,106 patients with low baseline FEV_1 of 200 to 1,621 mL, the percentage increase ranged from 12% to 44.7%—but was less than 200 mL, the currently accepted guideline value.

Bias was reduced when BDR was reported as a percentage of the predicted value or as a *z* score. With this approach, the 200 mL cutoff was redundant and positive responses were reduced by half. The change in FEV_1 percent from baseline was greater at higher levels of airway obstruction, but lower with severe obstruction when expressed as a *z* score or percent predicted. No matter how it was reported, change in FVC increased with level of airway obstruction.

Reporting BDR tests in terms of the percentage • • •

change in FEV_1 from baseline "spuriously suggests" that patients with more severe impairment have a greater response to bronchodilator. By comparison, expressing the results in terms of percentage of the predicted FEV_1 or FVC obviates the need for the 200 mL cutoff point and associated sources of bias. The authors conclude, "A critical evaluation of the FVC response is recommended in patients with severe airways obstruction."

COMMENT: This study examined more than 30,000 patients undergoing spirometry with bronchodilator testing. The authors conclude that postbronchodilator responses should be assessed as a percentage of the predicted value, not relative to baseline (as we currently do) as the latter introduces a bias associated with age, height, sex, gender and ethnicity. They also point out that the FVC response to bronchodilation is more important in patients with severe obstruction. A postbronchodilator fall in FEV_1 or FVC is common and likely related to spontaneous variability in repeated measurements.

D.A.K.

Quanjer PH, Ruppel GL, Langhammer A, et al: Bronchodilator response in FVC is larger and more relevant than FEV_1 in severe airflow obstruction. Chest. 2017;151:1088-1098.

Keywords: bronchodilator responsiveness, diagnosis, spirometry

Overprescription of Oral Steroids for Asthma

There are concerns about overuse or oral corticosteroids (OCS) for children with asthma exacerbations. This study examined rates of OCS dispensing among children with asthma in a Medicaid managed care program, including factors associated with variations in OCS use.

The analysis included 69,056 children with asthma, younger than 18 years, enrolled in the Texas Children's Health Plan from 2011 to 2015. In each year, more than 40% of children had at least one OCS dispensing, with a range of 42.1% to 44.2%. Multiple dispensings were common, especially to children aged 1 to 4.

More than 80% of children dispensed OCS did not have other characteristics of poor asthma control, such as excessive beta-agonist refills or hospital utilization. Children with a Board-certified pediatrician as their primary care practitioner were less likely to receive OCS. Among pediatricians, OCS prescribing rates varied from 15% to 86%. Pediatricians' OCS prescribing showed little association with emergency department visits, and none with hospital admissions.

Data from this Texas Medicaid managed care program suggest "substantial overprescribing" of OCS for children with asthma, especially in the preschool age group. Findings include substantial variation in OCS prescribing among practitioners, without evidence of poor asthma control.

COMMENT: Analysis of medication prescription patterns from a Medicaid and Children's Health Insurance Claims Data set in Texas showed that 1 in 4 children with asthma had at least one OCS-dispensing event: twice the frequency reported in other areas of the United States. Only 28% of children were dispensed inhaled corticosteroids (ICS), highlighting the concern regarding overprescribing of OCS and underprescribing of ICS for persistent asthma. Alas, attaining the goal of optimal asthma control remains elusive. (See the accompanying editorial: Pediatrics. 2017;139:e20170598.)

C.D.

Farber HJ, Silveira EA, Vicere DR, et al: Oral corticosteroid prescribing for children with asthma in a Medicaid managed care program. Pediatrics. 2017;139:e20164146.

Keywords: asthma (child), Medicaid, oral corticosteroids

REVIEWS OF NOTE

COMMENT: This is an excellent review of the factors that cause persistence of asthma from childhood to adulthood.

B.E.C.

Fuchs O, Bahmer T, Rabe KF, von Mutius E: Asthma transition from childhood into adulthood. Lancet Respir Med. 2017;5:224-234.

COMMENT: This informative review provides clinicians who prescribe FDA-approved drugs an excellent understanding of the key aspects of drug regulation.

C.D.

Gassman AL, Nguyen CP, Joffe HV: FDA regulation of prescription drugs. N Engl J Med. 2017;376:674-682.

COMMENT: Patch testing is increasingly important in allergy practice. Patients with biomedical device placement and new-onset allergic reactions can be a conundrum. In patients with a history of hypersensitivity to metals, the authors recommend patch testing prior to device implantation. Preimplantation testing may be beneficial for all patients undergoing Nuss bar placement, as pectus excavatum may be associated with a higher rate of metal allergy. For postimplantation patients, use of patch testing with lymphocyte transformation tests and histologic examination may help identify patients who need replacement of the biomedical device. There is a need for clear guidelines and studies of the utility of preimplantation and post implantation testing.

V.H.-T.

Rosner GA, Fonacier LS: Hypersensitivity to biomedical implants: prevention and diagnosis. Allergy Asthma Proc. 2017;38:177-183.