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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 Second 'MOC' Issue

The *AllergyWatch* editorial team is proud to share its second Maintenance of Certification issue, which highlights the July-December ABAI Continuous Assessment Program article list.

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

'MOC' ARTICLES

Head and Neck

Hui J, Ong J, Herdegen JJ, et al: Risk of obstructive sleep apnea in African American patients with chronic rhinosinusitis.
Ann Allergy Asthma Immunol. 2017;118:685-688.

Many patients with chronic rhinosinusitis (CRS) have poor sleep quality, and some of these have an associated diagnosis of obstructive sleep apnea (OSA). Recognition of patients at risk and early diagnosis are essential to implement effective treatment. This study evaluated risk factors for OSA among CRS patients seen at specialist clinics.

The retrospective study included 916 CRS patients seen at allergy or otolaryngology clinics. Of these, 100 had OSA diagnosed by polysomnography: a prevalence of 10.9%. These patients had a mean apnea-hypopnea index (AHI) of 32.63. Risk of OSA appeared higher in African American patients: 46% of patients with CRS and OSA were African American, compared to 20.22% of CRS patients without OSA.

The risk of OSA in African American patients with CRS remained significant on multivariable analysis: adjusted odds ratio (OR) 1.98. Risk was also elevated for patients with CRS without nasal polyps: OR 1.63, compared to patients with CRS with nasal polyps. Other comorbid conditions and variables associated with CRS were not associated with OSA.

African American patients with CRS appear to be at increased risk of OSA, compared to white patients. Patients with CRS without nasal polyps are also at high risk. The authors recommend screening for OSA in these groups of CRS patients.

COMMENT: This retrospective cohort found that African American patients had a higher risk for OSA than white patients. Patients with CRS without nasal polyps had a higher risk of OSA compared to those with nasal polyps. The authors suggest screening patients with CRS for OSA, particularly African Americans and those without nasal polyps.
S.M.F.

Campbell AP, Phillips KM, Hoehle LP, et al: Depression symptoms and lost productivity in chronic rhinosinusitis.
Ann Allergy Asthma Immunol. 2017;118:286-289.

Chronic rhinosinusitis (CRS) has a substantial impact on quality of life, comparable to that of asthma or cardiac disease. It also carries high healthcare costs as well as indirect costs due to lost productivity. The authors evaluated the impact of CRS on missed work and school days, including the role of specific symptoms and symptom patterns.

The prospective, cross-sectional cohort study • • •

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

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

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included 107 patients with CRS: mean age 52 years, 54% female, and predominantly white. Comorbid conditions included aeroallergen hypersensitivity in 41% of patients, asthma in 26%, and aspirin sensitivity in 23%. Sleep, nasal, otologic and facial pain, and emotional subdomain scores were calculated from responses to the 22-item Sinonasal Outcomes Test. Other assessments included nasal obstruction and depression risk and number of work and/or school days missed over the last 3 months.

Patients reported a mean of 3.1 missed days of work or school due to CRS. The emotional function subdomain was the most strongly associated with lost productivity. Sleep, nasal symptoms, and otologic and facial pain were unrelated to missed work/school days. On multivariable analysis, nasal obstruction symptoms were also related to lost productivity.

The study confirms the high burden of CRS in terms of missed days from work or school. Depression-related symptoms show the strongest association with lost productivity. Targeted treatment of depression symptoms and emotional functioning might lessen the productivity losses associated with CRS.

COMMENT: The FDA and most patients view rhinosinusitis as a nuisance and "over-the-counter" disease. This study shows us that patients with CRS have significant impairment in functionality. They miss an average of 3 days from work or school during the preceding 3 months and have problems with emotional function, depression, and loss of productivity. Depression will not only cause problems at work or school, but will also produce inadequate symptom reporting so that healthcare practitioners cannot respond appropriately.

B.E.C.

Stevens WW, Peters AJ, Hirsch AG, et al: Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract. 2017;5:1061-1070.

Patients with aspirin-exacerbated respiratory disease (AERD) have asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and intolerance of cyclo-oxygenase-1 inhibitor medications. The true prevalence of AERD among patients with CRSwNP and the burdens associated with this condition are unclear. The prevalence and unique clinical characteristics of patients with AERD were analyzed.

Analysis of electronic medical records at a tertiary medical center identified 1,059 patients with confirmed CRSwNP. Of these, 43% had CRSwNP only, 39% had CRSwNP plus asthma, and 16% had AERD. Age was similar among groups, but 62% of patients with AERD were women. Atopy was present in more than 80% of patients with AERD or asthma, compared to 66% of those with CRSwNP only.

Sixty-six percent of AERD patients were classified as having severe sinus disease, compared to 23% with CRSwNP plus asthma and 10% of the CRSwNP group. Patients with AERD had undergone twice as many sinus surgeries and were significantly younger at their first sinus surgery: mean age 40 years, compared to 43 years for those with CRSwNP only. Patients with AERD were also more likely to be corticosteroid-dependent: 13%, compared to 4% of patients with CRSwNP plus asthma and none with CRSwNP alone.

In this tertiary care sample, AERD is present in roughly 1 out of 6 patients with CRSwNP. The clinical course of patients with

AERD differs from those of aspirin-tolerant patients with CRSwNP, including more severe sinus disease, more sinus surgeries, and a higher prevalence of corticosteroid-dependent disease.

COMMENT: These observations regarding CRSwNP are significant, and help us to understand the role of AERD. The study shows the morbidity associated with this diagnosis and the risks that more courses of oral corticosteroid and more episodes of sinus surgery will be needed—especially in aspirin-sensitive patients with CRSwNP plus asthma. Fifteen percent of patients with CRSwNP and asthma were unaware that they had AERD, should be kept in mind when considering aspirin challenges. This very debilitating disease is difficult to treat, but may be helped with the current and future biologics coming to the US market.

B.E.C.

Dermatology

Paller AS, Kabashima K, Bieber T, et al: Therapeutic pipeline for atopic dermatitis: end of the drought?
J Allergy Clin Immunol. 2017;140:633-643.

For decades, the main treatments for atopic dermatitis (AD) have been topical corticosteroids and, in more severe cases, systemic immunosuppressive drugs. With ongoing advances in understanding the mechanisms of AD—particularly the Th2 immune pathway—new drug therapies are now under development. The authors summarize new medications "in the pipeline" for the treatment of AD.

The review covers a wide range of topical and biologic agents being evaluated as new therapies for AD; most are currently in phase 2 clinical trials. The topical phosphodiesterase 4 (PDE4) inhibitor crisaborole was approved for mild to moderate AD by the FDA in 2016. Other PDE 4 inhibitors are in development, along with an aryl hydrocarbon receptor agonist, Janus kinase (JAK) inhibitors, and topical agents targeting commensal organisms.

Dupilumab, a biologic agent targeting the IL-4/IL-13 receptor, received FDA approval for moderate to severe AD in 2017. Other biologics under development target IL-4 and IL-13, among other Th2 cytokines including thymic stromal lymphopoietin, IL-5, and IL-13, and itch-specific IL-31. Other agents target Th22/Th17 cytokines, which are present at increased levels in lesional skin. Several oral small-molecule inhibitors with inflammation-suppressing effects are under development, with targets including chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes, PDE4, histamine 4 receptor, and JAK. Agents targeting pruritus, including NK1R inhibitors, are also being studied.

These new therapies, targeting aspects of AD pathogenesis, may offer increased effectiveness with fewer side effects than immunosuppressive drugs. The authors highlight some priorities for ongoing research, including the involvement of immune pathways other than Th2 signaling and identification of subphenotypes that may respond to targeted topical and systemic agents.

COMMENT: Atopic dermatitis is not a simple skin disease, as we well know. While treatment options for AD patients seemed limited for some time, this review gives us hope that several new treatment options exist. The review discusses the different modalities, including topical treatment, biologics and anti-inflammatory medications. The authors also remind us that use of biomarkers may help guide the practitioner in identifying what options may be most useful for specific patients. These treatment options will undoubtedly improve the long-term outcomes of AD.

V.H.-T.

Fonacier L, Bernstein DI, Pacheco K, et al: Contact dermatitis: a practice parameter–update 2015.
J Allergy Clin Immunol Pract. 2015;3:S1-S39.

The practice parameter on contact dermatitis (CD) was last updated in 2006. The 2015 update of the CD practice parameter makes evidence-based recommendations relevant to the medical history, physical examination, patch testing, and management of patients with suspected CD.

Recommendations on clinical evaluation call for considering the diagnosis of allergic CD in patients with chronic dermatitis, eczematous or noneczematous. Patch testing is the gold standard for diagnosis; evaluation of contact allergens should include personal products and home and work exposures. Especially in patients with hand involvement, irritant as well as allergic causes should be considered. Recommendations for physical examination encompass patients with various clinical presentations, including periorbital rash, lip and perioral dermatitis, chronic inflammatory disorders of the oral mucosa, and scalp and neck dermatitis.

An extensive series of recommendations for patch testing are presented, including allergen series, test systems, and reading and interpretation of the results. In determining the relevance of reactions, the patient's clinical and exposure history should be considered. Recommendations for sources of exposure to clinically relevant allergens are addressed; for cosmetics and hygiene products, a few important chemical classes are the most common causes.

Other recommendations address patch testing for CD due to topical medications, drug hypersensitivity, metal sensitization, and patients with joint replacement failure. Special populations include children and patients with occupational CD. Treatment recommendations focus on avoidance measures, adjunct therapies, and prevention and education.

COMMENT: This practice parameter offers extensive information for the practitioner caring for patients with CD. The information regarding the differential diagnosis, interpretation of testing, and practical advice regarding treatment of these diseases is useful for the medical team. The review of the types of contact allergens that present a specific number of days after exposure is invaluable. The authors also

identify special situations in which testing should be considered, such as testing for metal allergens in some patients prior to surgery.

V.H.-T.

Druey KM, Parikh SM: Idiopathic systemic capillary leak syndrome (Clarkson disease). J Allergy Clin Immunol. 2017; 40:663-670.

Described by Clarkson in 1960, systemic capillary leak syndrome (SCLS) is associated with reversible hemoconcentration and hypoalbuminemia resulting from fluid and macromolecule leakage into tissues. The diagnosis and management of this rare, potentially fatal disease are reviewed, including some recent insights into its mechanism.

Less than 500 cases of SCLS have been reported since 1960, although 134 new cases were identified between 2010 and 2016. It is a sporadic condition reported most commonly in middle-aged white adults (median 48 years), with a slight female predominance (52%). Typical flares do not appear to result from usual allergy triggers. The classical acute form of SCLS is characterized by shock and anasarca caused by massive extravasation of up to 70% of total plasma volume. Flares vary in severity and frequency and may change over time. Patients may suffer a wide range of complications, including permanent disability resulting from compartment syndromes.

The diagnostic triad of SCLS consists of hypotension, hemoconcentration, and hypoalbuminemia (the "3 Hs"). In the recently reported series, more than two-thirds of patients (always adults) had monoclonal gammopathy of unknown significance. There are no specific biomarkers; the diagnosis remains a clinical one. The authors discuss their approach to diagnostic testing, evaluating other possible causes of hypotension and/or edema. The mechanism remains unknown, but there is evidence of humoral factors promoting vascular endothelial permeability during SCLS flares.

Treatment of acute SCLS consists of intravenous fluid therapy to manage intravascular volume depletion, maintain organ perfusion, and avoid severe metabolic acidosis. Treatment is primarily supportive; even severe SCLS attacks are self-limited. Since vascular leak resolves spontaneously after several days, it is difficult to analyze the efficacy of interventions. Intravenous immunoglobulin is a promising but nonspecific prophylactic treatment.

Allergists need to be aware of the possibility of SCLS, which can mimic angioedema, anaphylaxis, or other more common plasma leakage syndromes. The authors hope that recent advances in understanding of the pathogenesis of this condition will lead to new diagnostic, prognostic, and therapeutic approaches.

COMMENT: This is an excellent review of a condition that may present to the allergist/immunologist as a masquerader, and is important to consider in the differential diagnosis of anaphylaxis or angioedema. Because of the rarity of SCLS, evidence for treatment relies on observational data. Treatment for acute episodes is supportive. The authors recommend empiric prophylactic treatment with intravenous immunoglobulin for newly diagnosed cases.

D.M.L.

Lung

**Nair P, Wenzel S, Rabe KF, et al: Oral glucocorticoid-sparing effect of benralizumab in severe asthma.
N Engl J Med. 2017;376:2448-2458.**

Benralizumab is a monoclonal antibody against the alpha subunit of the interleukin-5 receptor, producing rapid depletion of eosinophils via natural killer cell-mediated, antibody-dependent cellular cytotoxicity. The ZONDA trial evaluated benralizumab's effect on oral glucocorticoid requirement in patients with severe asthma and persistent blood eosinophilia.

The trial included 220 adults with severe asthma and persistent eosinophilia, all continuously treated with oral glucocorticoids for at least 6 months. Patients were randomly assigned to treatment with subcutaneous placebo or benralizumab. The benralizumab dose was 30 mg every 4 weeks or every 8 weeks; in the 8-weekly dose group, the first three doses were given every 4 weeks. At the end of the 28-week intervention period, the rate of reduction in oral glucocorticoid dose while maintaining asthma control was assessed, along with secondary outcomes.

The two benralizumab groups achieved a 75% median reduction in the final glucocorticoid dose, compared to a 25% reduction in the placebo group. Thirty-three percent of the 4-weekly dose group and 37% of the 8-weekly dose group had at least a 90% reduction in oral glucocorticoid dose, compared to 12% of the placebo group. The two benralizumab groups also had reductions in the annual exacerbation rate of 55% and 70%, respectively, compared to placebo. The 8-weekly benralizumab dose was associated with improvements in asthma control and asthma-related quality of life. Pulmonary function measures and adverse effects were similar between groups.

Benralizumab reduces oral glucocorticoid requirement while maintaining asthma control in adults with severe asthma and persistent eosinophilia. About 20% of patients had no reduction in oral glucocorticoid dose with benralizumab, despite having baseline blood eosinophil counts similar to those of patients with large reductions in glucocorticoid dose.

COMMENT: The ZONDA examined the effects of benralizumab in a population of steroid dependent asthmatics with baseline eosinophil counts of greater than 150 cells/mm^3. After 28 weeks, active treatment resulted in a fourfold greater likelihood of oral glucocorticoid dose reduction, with half of the eligible subjects able to discontinue oral corticosteroids completely. Patients in the active arm had substantially fewer exacerbations and exacerbation-related

hospitalizations. It should be noted that 20% of these subjects were unable to reduce their oral glucocorticoid dose and that active therapy was not associated with improvement in FEV_1.

J.J.O.

Guilbert TW, Colice G, Grigg J, et al: Real-life outcomes for patients with asthma prescribed spacers for use with either extrafine- or fine-particle inhaled corticosteroids.
J Allergy Clin Immunol Pract. 2017;5:1040-1049.

The use of valved holding chambers, or spacers, has long been recommended to aid in coordinating device activation with inhalation for asthma patients using pressurized metered-dose inhalers (pMDIs). However, little is known about the real-world effectiveness of using a pMDI with a spacer. This issue was addressed in a historical matched cohort study comparing patients prescribed extrafine- or fine-particle inhaled corticosteroids (ICS) with and without a spacer.

Using UK databases, the researchers identified two matched groups of 1,840 adolescent or adult (12 years or older) asthma patients prescribed inhaled beclomethasone dipropionate via pMDI, with or without a spacer; and matched groups of 412 patients prescribed fluticasone propionate, with or without a spacer. Exacerbation rates and other asthma-related outcomes were compared for patients using ICS with or without a spacer.

Over 1 year, the use of a spacer had no significant effect on severe exacerbations: with or without a spacer, about 10 percent of patients had one or more severe exacerbations. With both types of ICS, most secondary outcomes were also similar with or without a spacer: acute respiratory event rate, risk-domain asthma control, and oral candidiasis diagnosis or treatment. Spacer use was associated with lower odds of overall asthma control: odds ratio 0.85 in patients using extrafine-particle and 0.63 in those using fine-particle ICS. This difference was likely related to a slightly higher rate of short-acting beta-agonist prescribing in the spacer groups.

These matched historical cohort studies question whether adding of a spacer improves asthma outcomes for patients received extrafine- or fine-particle ICS. The authors emphasize the importance of proper technique and patient adherence in optimizing the outcomes of ICS therapy for asthma.

COMMENT: This real-life study has significant flaws that limit the generalization of the results. First, even though the spacer was prescribed, there is no evidence for medication adherence or use of the spacer. The inhaled therapies are highly dependent on proper technique. Although there was a significant difference that favored patients who were reportedly not using spacers, the ability to generalize these data to a single patient is at best speculative.

B.E.C.

Corren J, Parnes JR, Wang L, et al: Tezepelumab in adults with uncontrolled asthma. N Engl J Med. 2017;210:936-946.

Tezepelumab is an investigational IgG2 monoclonal antibody that binds to the epithelial cell-derived cytokine thymic stromal lymphoprotein (TSLP). In a proof-of-concept study, tezepelumab inhibited early and late asthmatic responses and suppressed markers of type 2 inflammation in response to allergen challenge in patients with mild allergic asthma. The PATHWAY trial assessed the efficacy of tezepelumab in patients with uncontrolled asthma.

The multicenter trial included 584 adults who had uncontrolled asthma despite treatment with long-acting beta-agonists (LABAs) and medium- to high-dose inhaled corticosteroids (ICS). Patients were randomly assigned to 52 weeks of subcutaneous tezepelumab, 70 mg every 4 weeks, 210 mg every 4 weeks, or 280 mg every 2 weeks, or placebo. The primary efficacy endpoint was annualized asthma exacerbation rate. Outcomes were assessed in subgroups defined by high versus low blood eosinophil counts (based on a cutoff of 250 cells/μL) and markers of Th2 status

All three tezepelumab groups had a significant reduction in asthma exacerbation events per person-year: 0.26, 0.19, and 0.22 in the low-, medium-, and high-dose groups, compared to 0.67 in placebo controls. Reductions in exacerbation rates were 61%, 71%, and 66%, respectively, with similar improvements in patients with high versus low blood eosinophil counts at baseline.

Tezepelumab led to significant reductions in blood eosinophils, exhaled nitric oxide, and total serum IgE. Prebronchodilator FEV_1 was also higher with tezepelumab, with differences of 0.12 L in the low-dose group, 0.11 L in the medium-dose group, and 0.15 L in the high-dose group.

This phase 2 trial shows a reduced exacerbation rate in adults with uncontrolled asthma treated with the TSLP blocker tezepelumab. The benefits are independent of baseline eosinophil count and other inflammatory biomarkers. The investigators conclude, "These findings highlight the potential advantages of targeting an upstream cytokine such as TSLP, which may affect disease activity more broadly than inhibition of a single downstream pathway."

COMMENT: Available biologic agents target the Th2-high asthma population. This study examines the impact of tezepelumab, which blocks TSLP: an epithelial cell-derived cytokine that upregulates production of cytokines by antigen-specific Th2 cells. Because TSLP is an upstream cytokine and may have broader effects on asthma, this study examined uncontrolled asthma patients with both high and low eosinophil counts. Following 52 weeks of therapy, tezepelumab reduced the annualized rate of asthma exacerbations, independent of both baseline eosinophil count and other Th2 biomarkers (IgE and exhaled NO).

J.J.O.

Food and Drug Allergy/Hypersensitivity Reactions

Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139:173-181.

Oral immunotherapy (OIT) is a promising new treatment option for peanut allergy, despite disadvantages related to treatment withdrawal and reversibility of desensitization. Children recently diagnosed at preschool age might have clinical and immune profiles associated with an increased chance of treatment success. A randomized controlled trial of early OIT for infants and toddlers with newly diagnosed peanut allergy is reported.

The study included 40 children, aged 9 to 36 months: 31 with clinical peanut allergy and 9 who were sensitized but never exposed. The children were assigned to low-dose or high-dose OIT, with target maintenance doses of 300 or 3,000 mg/d, respectively. They continued OIT for 3 years, or until they met four specified criteria. The primary outcome was sustained unresponsiveness at 4 weeks (4-SU) after stopping OIT, based on double-blind, placebo-controlled food challenge. Outcomes were compared to those in 154 matched controls receiving standard care.

On intention-to-treat analysis of 37 children at a median of 29 months, both OIT regimens were associated with high rates of the primary outcome: 85% in the low-dose group and 71% in the high-dose group. On per-protocol analysis, 29 of 32 children (91%) achieved the 4-SU outcome. Peanut-specific IgE levels decreased significantly in the early OIT group, compared to a significant increase in the retrospective control group. Children receiving early OIT were much more likely to have successful peanut consumption: relative risk 19.42. Despite a high rate of allergic side effects, early OIT was safe and well tolerated.

Early OIT appears to be a safe and effective strategy for preschool-aged children recently diagnosed with peanut allergy. High rates of sustained tolerance and reduced peanut-specific IgE levels are achieved with target maintenance doses of 300 or 3,000 mg/d. Both low- and high-dose OIT are associated with high rates of sustained responsiveness and modulation of allergic immune responses.

COMMENT: Patients with food allergy need options other than avoidance. This study supports the safety and efficacy of OIT to peanut in young children during the preschool years. The authors remind us that this may be an exciting option for young children with food allergy and their parents, who may otherwise be limited in their diets and fear life-threatening reactions. This may be especially important during the early years, when children may not be able to verbalize their symptoms. Further studies will continue to follow patients who have received OIT over time.

V.H.-T.

Jones SM, Burks AW: Food allergy. N Engl J Med. 2017;377:1168-1176.

An estimated 15 million Americans—approximately 4% of children and 1% of adults—are affected by food allergies. Peanut allergy, affecting about 1% of Americans, is the most frequent cause of fatal and near-fatal anaphylaxis. The authors review the clinical problem of food allergy, along with strategies and evidence regarding its clinical management.

The authors review current strategies for evaluation, prevention, and management of food allergy. Dietary and medical management includes careful avoidance of the allergenic food, with ongoing education and scheduled follow-up. Epinephrine is the initial drug of choice, but remains "vastly underprescribed and underutilized." Once anaphylaxis occurs and/or epinephrine is administered, emergency medical services should be activated for transport to an emergency care facility.

Over the past decade, advances have been made toward developing allergen-specific immunotherapies for food allergy. The three main routes of immunotherapy—oral, sublingual, and epicutaneous—each target a different aspect of the mucosal surface. The authors review current evidence for these treatments, which remain experimental. Recent evidence suggests that dietary introduction of peanut in the first year of life can reduce the risk of peanut allergy for many children. The authors target some important areas for further research, including the need for more effective diagnostic approaches. Data on the long-term effectiveness of oral immunotherapy will be needed as well.

COMMENT: This clinical practice review begins with a case vignette of a peanut-allergic patient with anaphylaxis after an accidental ingestion. Pertinent points include the top eight allergenic foods (milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish) and risk factors for the most severe allergic reactions (delayed treatment with epinephrine, adolescent/young adult age, allergy to peanuts, tree nuts, fish or shellfish). Other risk factors include exercise, viral infection, menses, emotional stress, alcohol and medical conditions such as asthma, mastocytosis and treatment with beta blocker or ACE inhibitor.

S.M.F.

Coop CA, Schapira RS, Freeman TM: Are ACE inhibitors and beta-blockers dangerous in patients at risk for anaphylaxis? J Allergy Clin Immunol Pract. 2017;5:1207-1211.

There is continued controversy over the possible increase in anaphylaxis risk associated with antihypertensive medications: specifically, angiotensin converting enzyme inhibitors (ACEIs) and beta-blockers. The authors review current evidence on the mechanisms of ACEIs and beta-blockers and their effects in patients at risk for anaphylaxis.

During anaphylaxis, histamine release causes decreased peripheral vascular resistance, leading to activation of

the renin-angiotensin system. Previous reports have suggested that ACEIs may block this compensatory mechanism, thus intensifying anaphylaxis. Beta-blockers may mask the cardiac effects of anaphylaxis, with unopposed alpha-adrenergic activity leading to severe bronchoconstriction. Beta-blockers might also blunt the response to treatments for anaphylaxis, including epinephrine.

There are conflicting reports as to whether patients taking ACEIs or beta-blockers are at increased risk of anaphylaxis. The researchers analyze reports related to food allergy, radiocontrast media, or venom allergy; most of this evidence comes from case reports or retrospective studies. Beta-blocker or ACEI therapy is listed as a relative contraindication to skin testing, despite limited evidence. A large body of research supports the safety of these medications, when indicated, during the buildup and maintenance phases of venom immunotherapy. There are no conclusive data regarding the use of beta-blockers and/or ACEIs during elective aeroallergen immunotherapy.

The review highlights the weakness of current evidence on whether ACEIs or beta-blockers are associated with an increased risk of anaphylaxis. The authors recommend avoiding beta-blockers, and possibly ACEIs, for patients at risk of anaphylaxis who do not have cardiovascular indications for these medications. However, for patients with cardiovascular disease, this concern must be balanced against the demonstrated benefits of beta-blockers and ACEIs.

COMMENT: This concise review summarizes data on potential risk in patients at risk for anaphylaxis and concomitant use of ACEIs and beta-blockers. Unfortunately, most of the data on this topic is limited to case reports or retrospective studies and much of the data is conflicting. Nevertheless, it is important to keep in mind that for patients with cardiovascular disease, these medications have a favorable effect on mortality, even taking into account the possibility of anaphylaxis.

D.A.K.

Motosue MS, Bellolio MF, Van Houten HK, et al: Risk factors for severe anaphylaxis in the United States.
Ann Allergy Asthma Immunol. 2017;119:356-361.Anaphylaxis

Recent data from the United States and other countries suggest a rising rate of anaphylaxis-related hospitalizations. Clinical markers are needed to distinguish patients at risk of severe or fatal anaphylaxis from those with mild to moderate reactions who can safely be discharged home. Risk factors for severe anaphylaxis were analyzed using a large US database.

The researchers identified 38,695 patients with severe anaphylaxis seen at US emergency departments between 2005 and 2014. Of these, 11.6% had at least one of four severe anaphylaxis outcomes: hospitalization, 11.5%; ICU admission, 5.3%; endotracheal intubation, 1.5%; and near-fatal anaphylaxis, 0.45%.

Factors associated with severe anaphylaxis outcomes on multivariable analysis included age 65 years or older, odds ratio (OR) 3.15; medication triggering anaphylaxis, OR 1.50; cardiac disease, OR,1.56; and lung disease, OR, 1.23. Age over 65 was strongly associated with increased risks of ICU admission, OR 5.35; intubation, OR 5.62; and near-fatal anaphylaxis, OR 6.71. Factors associated with decreased odds of severe anaphylaxis included younger age, OR 0.60 for 0 to 4 years and 0.72 for 5 to 17 years; food triggers, OR 0.80; venom trigger, OR 0.66; and history of asthma, OR 0.93.

Severe anaphylaxis outcomes are present in nearly 12% of patients with anaphylaxis seen at US emergency departments. Age older than 65 is the strongest risk factor for severe anaphylaxis. Other important predictors include episodes triggered by medications and history of cardiac or lung disease.

COMMENT: This study makes the important observation that older patients have an increase in anaphylaxis. They may also have significant comorbidities. Use of antihypertensive medications, especially beta-blockers and ACEIs, can lead to increased severity of anaphylaxis; this was not accounted for in the study. There is also significant variation in the timing and composition of emergency treatment, which could of course lead to varying rates of hospitalization. Although this study does give us a directional signal about anaphylaxis, it is of little help in analyzing specific patient outcomes—especially in patients younger than 65 without an obvious medication causing anaphylaxis or a pre-existing cardiovascular or lung disease.

B.E.C.

Feldweg AM: Food-dependent, exercise-induced anaphylaxis: diagnosis and management in the outpatients setting.
J Allergy Clin Immunol Pract. 2017;5:283-288.

Patients with food-dependent, exercise-induced anaphylaxis (FDEIA) experience anaphylaxis triggered by the combination of food and exercise. This occurs even though the implicated food is tolerated in the absence of exercise. The diagnosis and management of FDEIA are reviewed, along with some recent findings regarding additional augmentation factors.

Symptoms of FDEIA can occur at any stage of exercise; typically, the patient ingested the culprit food within 4 hours before exercising. Symptoms can be highly unpredictable and usually resolve if the patients stops exercising. Wheat/grains and nuts are the foods most commonly implicated in Western populations. Exercise is the most common augmenting factor, but recent reports have shown that it is not essential for symptoms to develop. Some patients will experience symptoms if they ingest a larger amount of the culprit food. Many other augmenting factors have been identified, including medications, alcohol, infections, and high heat and humidity. The author suggests that the term "augmentation factor-triggered food allergy" might be more appropriate than FDEIA.

Suggested diagnostic criteria include a history of anaphylaxis occurring only when exercise is preceded by food ingestion, with evidence of specific IgE to the implicated food. A positive food plus exercise challenge confirms the diagnosis, but a negative challenge cannot exclude it. Management focuses on avoiding the culprit food before exercise, along with identification of other augmenting factors for the individual patient. Medications might play a role in preventing episodes of FDEIA, but no randomized trials have been performed. While FDEIA appears to be a persistent disease, most patients report fewer attacks over time—perhaps reflecting recognition of early symptoms, modification of exercise habits, and avoidance of triggering foods and augmenting factors.

COMMENT: Food-specific exercise-induced anaphylaxis has been characterized as a "1-2 combination," with reactions resulting from exercise and prior consumption of a specific food. However, recent data indicate that reactions may occur without exercise, implying that the critical combination is consumption of a culprit food combined with an augmentation factor. While exercise is the primary augmenting factor, others may include alcohol, nonsteroidal anti-inflammatory drugs, opiates, infections, aeroallergen exposure, and premenstrual or ovulatory phases of the menstrual cycle. So it may be more appropriate to label this condition as "augmentation factor-triggered food allergy." The author recommends avoiding culprit foods for 4 to 6 hours prior to exercise and identifying possible augmenting factors.

D.M.L.

Castells M: Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol. 2017;140:321-333.

Anaphylaxis is a life-threatening condition for which prompt recognition and immediate treatment are essential. The author reviews current best practices in the management and treatment of anaphylaxis in the era of precision medicine.

Recent definitions of anaphylaxis provide a mechanistic description based on phenotypes, with differing underlying endotypes supported by diagnostic biomarkers. Mature tryptase is released from mast cells and basophils within minutes of initial anaphylaxis symptoms. In commercial immunoassays, increases in tryptase level higher than the normal range of 11.4 ng/mL indicate acute mast cell/basophil activation. The current role of diagnostic tests is reviewed, including skin testing, specific IgE measurement, and the basophil activation test. An algorithm for anaphylaxis diagnosis is presented, addressing phenotype/triggers and an approach to biomarker findings linked to specific endotypes.

Anaphylaxis can have a major impact on the patient's quality of life, sometimes causing constant fear that can limit functioning. Epinephrine is central to acute treatment, administered when two or more organs are affected or there is laryngeal involvement or hypotension. The author discusses the efficacy and good safety record of desensitization in patients with anaphylaxis to chemotherapy drugs, monoclonal antibodies, and antibiotics.

Allergists have a critical responsibility for diagnosis and management of anaphylaxis, and for educating other healthcare providers in its symptoms, presentation, and acute management. Key areas for future research include clarification of new anaphylaxis phenotypes and endotypes, mast cell activation disorders presenting as anaphylaxis, biomarkers in addition to tryptase, and the role of tyrosine kinase inhibitors and other newer treatment modalities.

COMMENT: Because we are the experts in diagnosing and managing patients with anaphylaxis, this topic should be familiar to allergists. However, there are several new aspects to this review to freshen up the topic, including a proposed new mechanistic classification of anaphylaxis, a discussion of the role of the MRGPRX2 receptor, a review of Kounis and Takotsubo syndromes, and the use of KIT D816V mutations in the evaluation of anaphylaxis, to name a few.

D.A.K.

Immune Hypersensitivity Disorders

Allenspach E, Torgerson TR: Autoimmunity and primary immunodeficiency disorders. J Clin Immunol. 2016;36(Suppl 1):S57-S67.

With the identification of new primary immunodeficiency disorders (PIDD), it has become apparent that some of these conditions have a primary presentation of autoimmunity, rather than recurrent infections. Understanding of the molecular defects associated with these "immune dysregulation" disorders has led to identification of clusters that help in understanding some basic mechanisms leading to autoimmunity. This review focuses on three major themes resulting from this emerging body of evidence.

Some disorders are associated with abnormal responses to cellular or pathogen-derived debris, all of which can be linked to inappropriate inflammation caused by overproduction of type I interferons (IFNs). The excess type I IFN levels are associated with autoimmune and inflammatory conditions including lupus, vasculitis, and Aicardi-Goutieres syndrome. The authors discuss these mechanisms in more detail. Inappropriate responses to cellular debris with overproduction of type I IFNs are likely to be recognized as a mechanism of other immunodeficiency or immune dysregulatory disorders.

Other defects involve T-regulatory cells (Tregs) and Treg targets. The two main mechanisms by which Tregs suppress immune activation are direct cell-to-cell contact and bystander suppression mediated by immunoregulatory cytokines. The third theme involves defects that alter antigen receptor signal strength. Study of these disorders highlights the importance of hitting the "sweet spot" of T-cell or B-cell receptor signal strength—neither too weak nor too

strong—in the development of the adaptive immune system. The review also addresses various types of organ-specific autoimmunity in PIDD: autoimmune cytopenias, and autoimmune/inflammatory pulmonary disease, and enteropathy.

The review highlights the impact of autoimmune or inflammatory disease among patients with PIDD. Study of defects leading to autoimmunity is lending new insights into the mechanisms and pathways of immune dysregulation. Prompt recognition and treatment of autoimmune symptoms in patients with PIDD are essential to improving quality of life and reducing complications.

COMMENT: This thorough review discusses the fact that autoimmunity can be an important part of the presentation in some patients with PIDD. The authors remind us that signs and symptoms of autoimmunity may be present before, during, or after the diagnosis of PIDD. As we learn more about these diseases, it is imperative to keep this in mind in order to maximize the treatment of patients with PIDD. Improved diagnosis and consideration of comorbid autoimmunity and inflammation is necessary to improve patients' overall health and outcomes.

V.H.-T.

Kanneganti T-D: Inflammatory bowel disease and the NLRP3 inflammasome. N Engl J Med. 2017;377:694-696.

A recent experiment in mice (Neudecker et al: J Exp Med. 2017;214:1737-1752) provided insights into the role of a specific micro-RNA, miR-223, in the development of inflammatory bowel disease (IBD). The clinical implications of that basic science study are discussed, focusing on involvement of the NLRP3 inflammasome in IBD.

In the study, an epithelial irritant was used to induce colitis in mice. Animals deficient in miR-223 had higher expression of interleukin-1β (IL-1β) and associated chemokines, compared to wild-type mice. An IL-1R antagonist reduced inflammation, suggesting that the elevated IL-1β levels were likely pathogenic.

Interleukin-1β is activated by a protein complex called an inflammasome. Part of the inflammasome is the protein Nlrp3, which senses and responds to various "danger signals." The miR-223-deficient mice used in the study had enhanced expression of the Nlrp3 gene in the colon and myeloid cells.

The researchers concluded that miR-223 in inflammatory monocytes suppress the Nlrp3 inflammasome during episodes of acute colitis. In this model, miR233 downregulated Nlrp3 gene expression, "dampening" IL-1β maturation and resulting inflammation.

Gene variants encoding parts of the inflammasome have been linked to IBD, and deficiencies of these components are associated with susceptibility to colitis in mice. At the same time, overt activation of the inflammasome is associated with IBD and other inflammatory disorders.

COMMENT: The inflammasome is an important part of the innate immune system. Various inflammasome-related disorders are responsible for many autoinflammatory diseases including familial cold autoinflammatory syndrome. This brief review summarizes data from a study that explored the function of a specific micro-RNA, miR-223, known to be elevated in colon tissue of IBD patients. These investigators found that mice deficient in miR-223 were prone to colitis and produced more IL-1β and that colitis was improved with an IL-1R antagonist. Further experiments determined that miR-223 binds to NLRP3 (a protein in the inflammasome) and suppresses the inflammasome. The inflammasome is important for innate immunity but if overactive or underactive, it can lead to disease, including IBD. The moral of this story: a happy inflammasome yields a healthy colon.

D.A.K.

Andersen Y, Egeberg A, Gislason GH, et al: Autoimmune diseases in adults with atopic dermatitis.
J Am Acad Dermatol. 2017;76:274-280.

A growing body of evidence suggests that patients with atopic dermatitis (AD) are at increased risk of autoimmune disorders. This population-based study assessed the co-occurrence of selected autoimmune conditions among adults with AD.

Using nationwide Danish registries, the researchers identified 8,112 adults with an inpatient or outpatient diagnosis of AD and 40,560 non-AD controls matched for age, sex, and calendar time. Sixty-one percent of patients were women; the mean age was 42 years. History of smoking was more common in the AD group: about 14% versus 9%.

Atopic dermatitis was significantly associated with one-half of the autoimmune disorders considered in the study. These conditions, with their adjusted odds ratios, were: alopecia areata, 26.31; vitiligo, 17.98; chronic urticaria, 9.92; celiac disease, 5.19; chronic glomerulonephritis, 4.17; Sjögren syndrome, 3.74; systemic lupus erythematosus, 2.65; ankylosing spondylitis, 2.33; Crohn's disease, 2.09; unspecified inflammatory bowel disease, 2.07; ulcerative colitis, 1.64; and rheumatoid arthritis, 1.61. Associations were stronger among AD patients with a history of smoking.

The study supports the association between AD and autoimmune diseases, particularly in smokers. The associations might reflect common immunologic pathways and increased proinflammatory activation in patients with AD.

COMMENT: In this Danish case-controlled study of adult patients, a hospital diagnosis of AD was associated with 11 of 22 autoimmune diseases. Interestingly, there was a positive association between AD and gastroenterologic, dermatologic, and rheumatologic autoimmune conditions but not hematologic, neurologic, or endocrine autoimmune disorders. A history of smoking was also associated with a higher occurrence of comorbid autoimmune conditions. The authors suggest that patients with AD should be counseled about smoking and monitored for autoimmune diseases.

S.M.F.

Immunodeficiencies

Sullivan K, Bassiri H, Bousfiha AA, et al: Emerging infections and pertinent infections related to travel for patients with primary immunodeficiencies. J Clin Immunol. 2017;37:650-692.

With the global economy and easy air travel, visitors to foreign countries face a risk of emerging infections, infections specific to a particular country or region, and risks related to travel itself. These risks become critically important for travelers with primary immunodeficiency disorders (PIDD). The authors review infection risks and management issues specifically related to travel by patients with PIDD.

Several interrelated factors contribute to emerging infectious diseases around the world, including population growth trends, global warming, and changes in vector distribution. The authors discuss trends of special concern to patients with PIDD when traveling, including the safety and use of intravenous immunoglobulin products from other countries. Other key issues include strategies for diagnosis of infection in patients with deficient antibody responses, vaccine considerations, and emerging antimicrobial resistance, which varies widely around the world.

The review addresses a wide range of specific infections of concern in PIDD, with special attention to vector-borne infections. There are more than 100 arboviruses causing human disease; West Nile virus is the most common encephalitis arbovirus. Important non-neuroinvasive arborviruses include dengue, yellow fever, zika, and chikungunya.

The authors present detailed information on a wide range of infections of concern, including babesia, malaria, leishmania, rickettsiae, zoonoses, and human-transmitted viruses, bacteria, and mycobacteria, and various environmental exposures. Manifestations and infections unique to patients with immune deficiencies are discussed, including the wide range of phenotypes observed in PIDD and certain infections unique to specific types of PIDD.

The detailed review provides a basis for practical management of emerging infections and infectious concerns for the considerable population of PIDD patients with infections. The authors note that the landscape of infections is constantly changing; they provide a list of resource which specialists can access to obtain the latest information.

COMMENT: This review offers an important perspective for clinical immunologists, providing an overview of the impact of emerging global infections on patients with PIDD. There are several key "take-home" messages including that Candida, although a commensal, is still the most common infecting fungus in PIDD patients. It is important to avoid live viral vaccines in patient with PIDD. Severe measles has been reported in children with STAT2 and IFN-alpha/beta receptor deficiency since the type I interferon pathway is affected. Vaccine-associated paralysis is associated with oral polio vaccine, which is therefore contraindicated in both PIDD patients and their household contacts.

S.M.F.

**Walter JE, Farmer JR, Foldvari Z, et al: Mechanism-based strategies for the management of autoimmunity and immune dysregulation in primary immunodeficiencies.
J Allergy Clin Immunol. 2016;4:1089-1100.**

Patients with primary immunodeficiency (PID) are at risk of developing various autoimmune and inflammatory disorders. New insights into the mechanisms of autoimmunity in PID provide an opportunity for targeted therapies. The authors review mechanism-based strategies for addressing common autoimmune and inflammatory complications of PID.

Autoimmune cytopenias such as autoimmune hemolytic anemia (AHIA) are particularly frequent in patients with PID. Increasingly, second-line therapies for these conditions are selected according to the underlying immunopathologic mechanism. Rituximab has been proposed as standard second-line therapy targeting the B-cell pathology of autoimmune cytopenias associated with common variable immunodeficiency (CVID). Infection risk must be considered in CVID patients who are not receiving immunoglobulin replacement therapy. Bortezomib has shown promise as an alternative form of B-cell-targeted therapy. The review also addresses targeted treatments for T-cell pathology and for autoimmune cytopenias developing after immune reconstitution.

Targeted approaches may also be selected for PID patients developing various rheumatologic diseases. Belimumab, targeting B-cell-activating factor, is a newly approved agent for treatment of systemic lupus erythematosus. However, it has yet to be studied specifically in patients with CVID. The review also covers considerations related to targeting T-cell and innate immune pathology.

Gastrointestinal pathology in patients with CVID is notoriously difficult to treat. Anecdotal reports suggest responses to tumor necrosis factor-α and vedolizumab, which may inhibit Treg cell trafficking to the gastrointestinal mucosa. Sirolimus has been reported effective in patients with CTLA2 haploinsufficiency. Immunomodulation approaches may be successful in patients with inflammatory GI disease associated with chronic granulomatous disease.

Targeted therapies for PID should address not only the clinical spectrum of autoimmune disease, but also the underlying cause of the patient's immune dysregulation. New insights into the mechanisms of autoimmunity in PID improve patient care while contributing to knowledge of autoimmune and inflammatory disorders.

COMMENT: This is an excellent review on a challenging problem: managing autoimmune complications in patients who are already immunosuppressed. Through use of biologics, targeted immunosuppression, and in select cases immune reconstitution, the arsenal to manage these patients is growing. Unfortunately, the evidence for many therapies is based on theory and case reports. Well-designed clinical trials are needed to determine the optimal therapy for some of the more common autoimmune complications.

D.A.K.

Wirsum C, Glaser C, Gutenberger S, et al: Secondary antibody deficiency in glucocorticoid therapy clearly differs from primary antibody deficiency. J Clin Immunol.2016;36:406-412.

Secondary immunodeficiency, including secondary hypogammaglobulinemia, can occur as a side effect of glucocorticoid therapy for autoimmune disorders. In this situation, it can be difficult to distinguish between glucocorticoid-induced immune changes and common variable immunodeficiency (CVID). The prevalence and characteristics of secondary hypogammaglobulinemia due to glucocorticoid therapy were analyzed in a group of patients with giant cell arteritis (GCA) or polymyalgia rheumatica (PMR).

The study included 22 patients with GCA and 14 with PMR who were being treated with oral prednisone. Mean duration of glucocorticoid therapy was 31.2 months, with a mean daily prednisone dose of 7.5 mg. Serum immunoglobulin levels and B- and T-cell subsets were measured in this GCA/PMR group and in an age- and sex-matched group of patients without immunosuppressive therapy.

Antibody deficiency developed in 21 of 36 GCA/PMR patients during glucocorticoid therapy. Nineteen patients had at least one IgG measurement less than 7.0 g/L; in 13 patients, IgG was the only reduced isotype. Eight patients had sustained reduction of IgG for at least 6 months, including all patients with IgG levels less than 5.0 g/L. Hypogammaglobulinemia occurred in 68% of GCA patients and 29% of PMR patients.

Analysis of B- and T-cell subsets showed reduced circulating naive and transitional B cells but preservation of IgM, IgG, and IgA memory B cells. There were also significant reductions in CD4 memory and regulatory T cells and a few CD8 T-cell subsets. The B- and T-cell subsets were not correlated with serum immunoglobulin levels or with hypogammaglobulinemia.

This experience suggests that about one-fourth of patients receiving glucocorticoid therapy for GCA or PMR develop persistent humoral immunodeficiency. In most cases, these glucocorticoid-induced immune changes consist of isolated IgG deficiency with preserved IgA production and class-switched memory B cells. This pattern "allows for a robust diagnostic separation from patients with primary antibody deficiency like CVID," the researchers write.

COMMENT: In this set of patients with GCA and PMR on corticosteroid therapy, the authors found that primarily IgG was affected. They saw persistent reduction in about 50% of cases, especially those whose IgG dropped below 5.0 g/L. When significant reduction occurred, it was seen during the initial high-dose phase of corticosteroid treatment. The researchers suggest that IgG levels be checked near the end of this phase of therapy. In contrast to CVID, corticosteroid-induced immunoglobulin abnormalities generally result in isolated deficiency of IgG, with preservation of IgA production as well as switched memory B cell populations.

J.J.O.

Eosinophilic and Gastrointestinal Disease

Chen Y-YK, Khoury P, Ware JM, et al: Marked and persistent eosinophilia in the absence of clinical manifestations. J Allergy Clin Immunol. 2014;133:1195-1202.

Most patients with hypereosinophilic syndrome (HES) have clinical manifestations related to eosinophilic tissue infiltration. Recent reports have defined a group of patients who marked hypereosinophilia, absolute eosinophil count greater than 1,500/μL, but no clinical signs or symptoms. The authors report a follow-up study in a group of the patients with "hypereosinophilia of unknown significance" (HES_{US}).

Investigation of a series of 36 patients with marked, unexplained eosinophilia who were not receiving treatment identified 8 patients with HES_{US}. All were asymptomatic on initial evaluation and remained free of end-organ manifestations for at least 5 years (median follow-up 11 years). The clinical and immunologic findings were compared to those of 28 patients with symptomatic, platelet-derived growth factor alpha-negative HES and 27 healthy controls.

Peak AEC was 3,961/μL in the HES_{US} group and 5,122/μL in the symptomatic HES group. Surface expression of eosinophil activation markers was also similar between groups. Fifty percent of HES_{US} patients had aberrant or clonal T-cell populations, compared to 29% of symptomatic HES patients. Both HES groups had elevated levels of interleukin (IL)-5, granulocyte-macrophage colony-stimulating factor, IL-9, and IL-17A, compared to controls. Serum IgE and IL-13 levels were elevated only in patients with symptomatic HES.

This study identifies a small but significant proportion of HES_{US} cases in a series of patients with persistent marked hypereosinophilia. These patients, who have a clinically benign course, are indistinguishable at baseline from patients with untreated symptomatic HES. Although it appears that completely asymptomatic patients with AEC greater than 1,500/μL can be followed up without specific treatment, further study of their risk of progression to HES is needed.

COMMENT: Most patients with HES present with signs and symptoms resulting from eosinophilic tissue infiltration and require therapy to reduce the eosinophil load. This study demonstrates that there is a subset of patients with unexplained marked eosinophilia who have no clinical manifestations even over a 5-year period. The authors suggest that this subset of patients with elevated eosinophils who have a benign course can simply be followed closely, without therapy.

J.J.O.

Molina-Infante J, Arias Á, Alcedo J, et al: Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 study. J Allergy Clin Immunol. 2018;141:1365-1372.

Empiric elimination diets are effective for most patients with eosinophilic esophagitis (EoE), but their use is limited by the complexity of the diets and the need for multiple endoscopies. Up to three-fourths of patients are found to have just one or two food triggers, most commonly milk and wheat/gluten. This prospective study evaluated the efficacy and cost savings of a step-up empiric elimination diet for EoE.

The 2-4-6 study enrolled 130 patients with EoE, including 25 pediatric patients, at 14 Spanish and Italian centers. All underwent an initial 6-week diet eliminating two foods: milk and gluten-containing cereals. Criteria for remission were improvement in EoE symptoms and an eosinophil count of less than 15/hpf on esophageal biopsy. Nonresponders proceeded to a 4-food elimination diet, with additional elimination of eggs and legumes. If there was still no response, they proceeded to a 6-food elimination diet, further eliminating nuts and fish/seafood. In responders, foods were gradually reintroduced, followed by endoscopic re-evaluation.,

Ninety-seven patients completed all phases of the study. The 2-food elimination diet led to EoE remission in 43% of patients, with similar responses in adult and pediatric patients. In these responders, identified food triggers were milk in 52%, gluten-containing grains in 16%, and both milk and gluten in 28%. The remission rate increased to 60% in response to the 4-food elimination diet and 79% after the 6-food elimination diet. Of 60 patients who responded to the 4- or 6-food elimination diet, 91.6% had one or two food triggers. On food reintroduction in 64 patients, milk was identified as a food trigger in 81%, gluten in 43%, egg in 15%, and legumes in 9%. The step-up protocol reduced endoscopic procedures and diagnostic process time by 20%, compared to initial empiric 6-food elimination diet.

This step-up elimination diet approach has the potential to simplify dietary management of adults and children with EoE. More than 40% of patients achieve remission with an initial 2-food elimination diet, while a 4-food elimination diet identifies two-thirds of all patients with one or two food triggers. The step-up approach reduces the number of endoscopies and shortens the time to diagnosis of the dietary cause of EoE.

COMMENT: In this study, 2-food, 4-food, and 6-food elimination diets for EoE were associated with 43%, 60%, and 79% rates of efficacy, respectively. More than two-thirds of patients had one or two food triggers; consequently, most responders could be identified via a "step-up" protocol. These data imply that a step-up elimination diet can lead to remission of EoE while shortening the diagnostic process, requiring fewer endoscopies, and reducing the burden associated with adherence to more extensive elimination diets.

D.M.L.

Pannaraj PS, Li F, Cerini C, et al: Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. JAMA Pediatr. 2017;171:647-654.

Previous studies have reported differences in the gut microbiota between people who were and were not breastfed as infants, with the differences persisting into adulthood. Most studies have focused on infant stool; there are few data on vertical transfer of breast milk microbes from mother to infant. This study examined whether the bacterial communities of the breast milk and areolar skin transfer to the infant gut.

The prospective study included 107 healthy mother-infant pairs; samples were collected when the infants were a median of 40 days old. Bacterial communities of the breast milk, areolar skin, and infant stool were assessed by 16S ribosomal RNA gene sequencing. The amount and timing of breastfeeding and the age at introduction of solid foods were assessed as well.

Bacterial communities in the three types of samples differed in terms of composition and diversity. The infants' gut microbiome was more closely related to that of the mother's breast milk and skin, compared to a random mother. The diversity of bacteria in infant stool increased with age, reaching convergence between individuals by about 12 months.

On source tracking analysis over the first 30 days of life, infants who got at least 75% of their daily milk intake from breastfeeding received a mean of 27.7% of bacteria from breast milk and 10.3% from areolar skin. The diversity and composition of gut bacteria changed with proportion of daily breast milk intake in dose-dependent fashion, even after solid foods were introduced. The microbiome matured earlier when solid foods were introduced before age 6 months.

In the first month of life, bacteria from the breast milk and maternal skin account for nearly 40% of the gut bacteria in primarily breastfed infants. Transmission is compromised in infants who are not primarily breastfed. The effects of breastfeeding on the infant microbiome continue even after solid foods are introduced. The researchers add, "Furthermore, breast milk contributes bacteria associated with a decreased risk for developing allergic disease."

COMMENT: Colonization of the infant gut has been shown to be a complex process. This study demonstrates that bacterial communities in breast milk and areolar skin contribute to development of the infant microbiome.

D.M.L.