

The Journal of Allergy and Clinical Immunology: In Practice — 2016 Year in Review



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As editors, we concluded that it would be helpful to our readers to write a Year in Review article that highlights the Review, Original, and Clinical Communication articles published in 2016 in *The Journal of Allergy and Clinical Immunology: In Practice*. We summarized articles on the topics of asthma, rhinitis/rhinosinusitis, food allergy, anaphylaxis, drug allergy, urticarial/angioedema, eosinophilic disorders, and immunodeficiency. Within each topic, epidemiologic findings are presented, relevant aspects of prevention are described, and diagnostic and therapeutic advances are enumerated. Diagnostic tools described include history, skin tests, and *in vitro* tests. Treatments discussed include behavioral therapy, allergen avoidance therapy, positive and negative effects of pharmacologic therapy, and various forms of immunologic and desensitization management. We hope this review will help you, our readers, consolidate and use this extensive and practical knowledge for the benefit of your patients. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:218-36)

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Our goal for *The Journal of Allergy and Clinical Immunology: In Practice* is to “strive for the highest quality and clinical relevance of our content so that JACI: In Practice will have the greatest possible impact on the clinicians and clinical researchers who manage and study asthma, allergic and immunologic diseases.”¹ We believe that the articles published in *JACI: In Practice* in 2016 further that goal as well as the even more important goal of improving the quality of life of our patients.¹ This Year in Review article will summarize the Review, Original, and Clinical Communication articles published in the Journal in 2016 on the topics of adult and pediatric asthma (including asthma medication adherence and self-management), rhinitis/rhinosinusitis, food allergy and anaphylaxis, drug allergy, urticaria/angioedema, eosinophilic disorders, and immune deficiency (Table 1). Articles were also published in the Journal this past year on the topics of atopic dermatitis,^{2,3} contact dermatitis,⁴ venom immunotherapy,⁵ hypersensitivity pneumonitis,⁶ climate change and health,⁷ use of twitter by allergists,⁸ atopy and food addiction,⁹ and rash and rhinitis aboard the International Space Station.¹⁰

ASTHMA

Pediatric asthma

The fourth year of publication of *JACI: In Practice* began auspiciously with enlightening reviews on the lessons learned from the National Heart Lung and Blood Institute (NHLBI) and National Institute of Allergy and Infectious Diseases (NIAID) sponsored asthma networks’ clinical trials over the past decade. The Inner-City Asthma Consortium revealed insightful information about the risk factors for and treatment of asthma exacerbations of the high-risk understudied inner-city poor and minority child with asthma.¹¹ Specific risk factors included (1) allergic status and pulmonary function during all seasons, (2) the months immediately following an exacerbation, (3) atopy, and (4) the combination of allergic sensitization and specific allergen exposure, particularly to cockroach and rodents. Beneficial interventions that reduced exacerbations included (a) eradicating household allergens, although difficult to accomplish, (b) encouraging preemptive controller medication use in the summer months to prevent fall exacerbations, (c) applying National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3-directed therapy to potentiate increased asthma control, and (d) implementing the anti-IgE biologic omalizumab.¹¹

The clinical trials conducted by the Childhood Asthma Research and Education (CARE) Network and AsthmaNet provided key messages to understand and manage high-risk recurrent episodic wheezing in preschool children.¹² This wheezing phenotype evidences high morbidity during acute episodes with minimal to no symptoms between episodes. Daily low-dose inhaled corticosteroids (ICS) are effective at reducing exacerbations, but not modifying disease progression, in those with a high

Abbreviations used

AA- Alkylated androgens
AAAAI- American Academy of Allergy, Asthma and Immunology
ABPA- Allergic bronchopulmonary aspergillosis
ACT- Asthma Control Test
AERD- Aspirin-exacerbated respiratory disease
Alpha-gal- Galactose-alpha-1,3-galactose
CARE- Childhood Asthma Research and Education Network
CHARGE syndrome- Coloboma, heart disease, choanal atresia, growth/mental retardation, genitourinary malformations, ear abnormalities
COPD- Chronic obstructive pulmonary disease
CRS- Chronic rhinosinusitis
CU- Chronic urticaria
CVID- Common variable immune deficiency
DOCK8- Dedicator of cytokinesis 8
DRESS- Drug reaction with eosinophilia and systemic symptoms
ED- Emergency department
EGPA- Eosinophilic granulomatosis with polyangiitis
EoE- Eosinophilic esophagitis
FPES- Food protein-induced enterocolitis syndrome
HAE- Hereditary angioedema
HES- Hypereosinophilic syndromes
ICD-9- International Classification of Disease, Ninth Revision
ICS- Inhaled corticosteroids
LABA- Long-acting β_2 -agonists
LTE4- Leukotriene E4
MCID- minimal clinically important difference
NAID- NOD2 associated inflammatory disease
NAEPP- National Asthma Education Prevention Program
NOD2- Nucleotide-binding oligomerization domain containing 2
NSAID- Nonsteroidal anti-inflammatory drug
OCS- Oral corticosteroids
OFC- Oral food challenge
PID- Primary immunodeficiency disease
RDD- Rapid drug desensitization
SABA- Short-acting β_2 -agonists
SLIT- Sublingual immunotherapy
SCIT- Subcutaneous immunotherapy
STAT-1- Signal transducer and activator of transcription 1

modified asthma predictive index. Intermittent high-dose ICS at the onset of respiratory illnesses was shown to be an alternate effective approach in this phenotype, with less cumulative ICS exposure. Children with atopic manifestations and greater disease burden appear to be particularly responsive to ICS.¹²

A secondary analysis of the CARE Network "Treating Children to Prevent Exacerbations of Asthma" trial found that the following baseline markers or characteristics were associated with reduced exacerbations in response to low-dose ICS treatment in 288 children aged 6 to 18 years with mild persistent asthma: non-Hispanic ethnicity, aeroallergen sensitization, elevated total serum IgE level (≥ 350 serum kU/L), and prior year oral corticosteroid (OCS) use for an asthma exacerbation.¹³ Markers associated with more asthma control days in the outcome year

during ICS treatment included male sex, aeroallergen sensitization, elevated serum IgE level, and partial control during run-in. Children with mild persistent asthma achieved greater benefit with ICS treatment if they evidenced atopic asthma or greater disease burden.¹³

Severe asthma in children, as in adults, occurs in a minority of asthmatics, but is complex, heterogeneous, and a challenge to treat. Dr. Fitzpatrick summarized findings from the subset of children enrolled with severe or refractory asthma in the Severe Asthma Research Program.¹⁴ This subset of children required high-dose ICS and occasionally systemic corticosteroids due to suboptimal control on usual doses of controller medications. These children had several phenotypes and likely biologic endotypes. They evidenced recurrent and life-threatening exacerbations, impaired quality of life, and increased medication-related adverse effects.¹⁴ Given that repeated OCS courses were associated with adverse effects, determining whether such treatment was beneficial for preschool children with acute episodic wheezing is important. In a Pro/Con debate that analyzed published studies on the role of OCS for acute wheeze in preschool children, it was concluded that, due to conflicting studies, there is an urgent need to conduct efficacy trials of OCS in toddlers with this wheezing phenotype.¹⁵

Interestingly, in a study of 499 urban children 5 to 17 years of age with asthma, elevated mouse specific-IgE but not household mouse allergen exposure was reported as an independent risk factor for rhinitis.¹⁶

A systematic review of the literature dealing with behavioral interventions to improve asthma outcomes among adolescents identified 24 articles that met the inclusion criteria. Approaches that were found to improve asthma self-management and adherence to daily controller medications included school-based interactive learning and direct observation of medication intake. The message to allergists/immunologists is to objectively monitor ICS use and provide feedback to improve adherence.¹⁷

Health-related quality of life during adolescence is impaired in asthma, particularly in those with uncontrolled asthma.¹⁸ Given the usual challenges with adolescence even in the absence of illness, greater attention is needed to improve asthma control in adolescence to enhance the quality of life of adolescents and allow them to better deal with adolescent challenges.

Although asthma specialist care improves asthma outcomes, largely unknown is the impact of the quality of asthma care provided by primary care physicians. Large variations in asthma care were documented across 22 primary care practices responsible for the care of 948 children aged 6.9 ± 2.7 years (21.6% <5 years old) with asthma.¹⁹ Asthmatic children receiving care from practices that provided preventive and acute asthma care experienced significantly more symptom-free days and also fewer asthma emergency department (ED) visits and hospitalizations, after controlling for potential confounders. Clearly, primary care physicians need to adopt guideline recommendations to improve outcomes in their patients with asthma.

Adherence remains a major obstacle for optimal care. A newly recognized reason for poor adherence was reported among 740 families in which there was a mismatching in half of the families between parent reports and physician intentions regarding ICS use.²⁰ Factors associated with this mismatching included Latino ethnicity, household smoking, or impressions that ICSs were ineffective. Improved communication between provider and parent is necessary to reduce these inconsistencies in ICS use.

Although much less common than in adults, aspirin-exacerbated respiratory disease (AERD) must be considered in asthmatic children with specific comorbidities. Aspirin challenges confirmed AERD in a case series of 3 patients aged 7, 12, and 16 years with asthma and concomitant nasal polyps and cyclooxygenase-1 inhibitor intolerance.²¹ Diagnosis of AERD allows disease-targeted therapies.

Castro-Rodriguez et al²² reviewed the evidence for risk and protective factors for childhood asthma. They examined 41 systematic reviews meeting inclusion criteria that focused on prenatal factors (n = 9), perinatal factors (n = 5), and postnatal factors (n = 27). Identified as unequivocal and previously recognized risk factors for childhood asthma were parental asthma, prenatal environmental tobacco smoke exposure, and prematurity (especially very preterm birth). Their systematic review also noted several modifiable behaviors or exposures with mild-moderate causal associations with childhood asthma. These included maternal prenatal factors (weight gain or obesity, antibiotic or acetaminophen use, and stress), perinatal factors (Caesarian births), and postnatal factors (severe respiratory syncytial virus infection, obesity, indoor mold exposure and outdoor air pollution).²² Further intervention or prospective studies are needed for confirmation. In addition to being a possible causative risk factor for childhood asthma as noted above, obesity contributed to an almost 1.6-fold increased odds for mechanical ventilation, increase in cost (almost \$1,600), and longer mean length of stay in a study of 70,844 asthma hospitalizations in children 2 to 18 years of age.²³

Adult asthma

Validation studies of several tools to help in asthma management were published this past year in the Journal. Globe et al²⁴ validated the psychometric properties of the daily Asthma Symptom Diary and reported its minimally important difference to help in determining symptom outcomes in clinical trials of persistent asthma.²⁴ The Pregnancy Asthma Control Test, a modified version of the Asthma Control Test (ACT), was validated by telephone in 159 pregnant asthmatics, and now can be used clinically to monitor these patients.²⁵

Lung sound analysis, a simple, noninvasive, and reproducible technique, was shown to correlate with airway inflammation and bronchodilator responsiveness in 31 adults with mild-to-moderate asthma.²⁶ Its clinical utility compared with spirometry requires further study.

Studies on risk factors for worse outcomes in adult asthma were reported, including depression, hypertension, chronic sinusitis, female sex, obesity, and beta receptor polymorphisms. A cross-sectional study of 20,271 adults using the 2007-2012 National Health and Nutrition Examination Survey reported that depressive symptoms were associated both significantly and linearly with asthma and independent of anxiety and other potential confounders.²⁷ Importantly, among asthmatics, bronchodilator response was significantly reduced in those with major depression. In a retrospective case-control analysis of almost 120,000 adult asthmatics evaluated in a large health maintenance organization, compared with controls without hypertension, those asthmatics with hypertension displayed evidence in multivariable analyses of enhanced asthma morbidity, including excessive rescue bronchodilator use, asthma ED visits or hospitalizations, and OCS dispensed.²⁸ An increased risk for asthma hospitalizations was reported among African Americans with

refractory chronic rhinosinusitis who evidenced a distinct phenotype of nasal polyposis, anosmia, and AERD in a retrospective database of 1344 patients with chronic rhinosinusitis.²⁹ Among a national representative sample of 4.3 million ED visits for asthma exacerbations, sex differences were reported in the frequency of hospitalizations.³⁰ Females among young children aged 4 to 11 years and adults 18 to 64 years evidenced increased risk for hospitalization, whereas the reverse was seen for females 12 to 17 years of age, after adjusting for confounders. The increase in disease burden associated with obesity might be explained, in part, by the corticosteroid pharmacokinetic abnormalities reported in obese and overweight corticosteroid-resistant asthmatics.³¹ Finally, homozygosity for the Arg/Arg polymorphism of the adrenergic beta-2 receptor was reported to be associated with the severity of allergic asthma, comparing a cohort with severe (n = 33) to mild-to-moderate (n = 51) asthma based on Global Initiative for Asthma step-care needed for asthma control.³² Future studies are needed to determine whether genetic polymorphisms will be useful in phenotyping patients with asthma.

In a real-world managed-care setting, the clinical and economic burden of the 2.3% of patients with severe uncontrolled asthma was determined among a cohort of 25,935 adolescents and adults with persistent asthma.³³ During a year of follow-up in this retrospective study, severe uncontrolled patients, despite high-dose controller therapy, exhibited significantly more asthma exacerbations, excessive short-acting β_2 -agonist (SABA) use, and higher all-cause and asthma-related costs than patients with nonsevere uncontrolled asthma.³³ Asthma medications accounted for the major difference in incremental costs in total asthma-related costs. The disease burden of adult patients with persistent asthma who also are diagnosed with chronic obstructive pulmonary disease (COPD) was also reported using a large retrospective administrative database.³⁴ Compared with patients with persistent asthma only, patients with persistent asthma and a COPD diagnosis exhibited significantly more comorbidities (gastroesophageal reflux disease, pneumonia, chronic sinusitis, and nasal polyposis), more indices for uncontrolled asthma based on impairment and risk, and concomitant higher intensity of asthma treatment. In addition, elevated blood eosinophil levels in patients with persistent asthma and a COPD diagnosis were an independent risk factor for future asthma exacerbations, suggesting a common inflammatory component between patients with persistent asthma with or without a COPD diagnosis.³⁴

AERD represents an important asthma phenotype. To extend the utility of spot urinary leukotriene E4 (LTE4) to evaluate respiratory disease, Divekar et al³⁵ demonstrated that 24-hour LTE4 determination was a reliable and simple test to perform as a predictor for AERD. A LTE4 cutoff value of 166 pg/mg creatinine exhibited 92% specificity to diagnose "challenge-confirmed" aspirin sensitivity.

In a population-based retrospective case-control study of 543 patients with incident myocardial infarction and matched controls without myocardial infarction, active asthma was significantly associated with incident myocardial infarction (odds ratio [OR] 2.3, 95% confidence interval [CI], 1.1-4.8), after multiple covariate adjustments including COPD.³⁶ Confirmation is needed to assess the relationship of asthma control and medications to the risk of myocardial infarction.

Omalizumab, an anti-IgE, has served as a valuable biologic for the treatment of moderate-to-severe uncontrolled asthma despite

high-dose conventional controller medication in adults and children. Determining candidacy for and dosing of omalizumab therapy is based, in part, on the serum level of total IgE. Hatipoglu et al³⁷ reported variability of serum IgE when measured every 2 months in 17 moderate-severe adults with allergic asthma. The probability of experiencing at least a 10% change was 69%, and clinical decisions in determining candidacy for treatment or dosing would have been affected by IgE variability in 7 of 17 (41%) patients.³⁷ Although investigational, omalizumab therapy has been reported to be effective in allergic bronchopulmonary aspergillosis (ABPA) in a randomized placebo-controlled trial.³⁸ More recently, exacerbations of ABPA while on omalizumab therapy in 3 patients were associated with at least doubling of total serum IgE levels,³⁹ and in another case report, effectiveness following omalizumab therapy for ABPA was accompanied by a substantial reduction of total serum IgE.⁴⁰ These findings support monitoring serum IgE during omalizumab treatment of ABPA, although larger confirmative studies are needed. Omalizumab has also been reported this past year to be effective in a 68-year-old woman with refractory vasospastic angina associated with peripheral eosinophilia, asthma, and chronic rhinosinusitis.⁴¹

Asthma treatment was highlighted in several 2016 Journal articles. Broccoli sprouts, the richest source of sulforaphane, an enhancer of antioxidant gene expression, was found not to improve fractional exhaled nitric oxide levels, spirometry, ACT scores, rhinitis quality of life scores, or oxidative stress biomarkers in a pilot double-blind, placebo-controlled study in adults with allergic asthma.⁴² A randomized sham controlled 40-week study of 247 adults and children with controlled persistent asthma reported that comprehensive individualized household allergen avoidance intervention significantly reduced all measured allergen levels of cat, dog, and dust mite in the bedroom and cockroach and mouse in the kitchen and bedroom.⁴³ Unfortunately, there was no significant reduction in the NAEPP-based step-care level, emphasizing the challenges in improving asthma outcomes with environmental intervention.

The long-acting antimuscarinic agent tiotropium received FDA approval for the treatment of asthma in September 2015. A double-blind, placebo-controlled phase III 12-week dose ranging study demonstrated the bronchodilator efficacy, safety, and tolerability of tiotropium at once daily dosage of 2.5 mcg and 5 mcg delivered as Respimat as add-on therapy to low- to medium-dose ICS in adults with uncontrolled asthma.⁴⁴ Both dosages significantly increased forced expiratory volume in 1 second and peak flow rates compared with placebo, extending the documentation of the benefit of tiotropium to uncontrolled adult asthmatics on low- to medium-dose ICS.

In a post hoc analysis of lung function during a 12-week clinical trial of 386 patients with moderate-to-severe asthma receiving either a combination ICS/long-acting β_2 -agonist (LABA), monotherapy ICS, monotherapy LABA, or placebo budesonide, fixed airway obstruction was found to be persistent in 29%, inconsistent in 31%, and not fixed in 40%.⁴⁵ Study withdrawal due to predefined adverse asthma events was more frequent in patients with persistent or inconsistent fixed airway obstruction.

Asthma is an important component of the syndrome of eosinophilic granulomatosis with polyangiitis (EGPA), previously called the Churg-Strauss syndrome. Latorre et al⁴⁶ described 37 patients with EGPA who were in partial or complete remission

from their systemic involvement on low dose OCS and immunomodulating drugs. Of note was that, although their systemic symptoms were controlled, poorly controlled asthma was documented in 21 patients (56.7%), and half of these patients were not receiving inhaled corticosteroids. Almost all patients demonstrated nasal disease as well. The authors recommend specific monitoring and targeted treatment to control respiratory disease in patients with EGPA.

Asthma associated with mold exposure has long been a major challenge in clinical care. To increase knowledge and clinical skills regarding this important topic, we published the May/June 2016 theme issue on Mold Allergy. The Clinical Commentary reviews in this issue comprehensively described (a) the updated taxonomy classification of allergenic fungi,⁴⁷ (b) the innate and adaptive immune responses to fungal products,⁴⁸ (c) the spectrum of health effects of fungi on people,⁴⁹ (d) the clinical evaluation and management of patients with suspected fungus sensitivity,⁵⁰ (e) guiding principles to determine when home assessments for potential mold exposure are warranted,⁵¹ and (f) specific home assessment and remediation activities.⁵²

Asthma medication adherence and self-management

It is a truism that without reasonable adherence to treatments, control of chronic disease remains futile, and asthma is no exception. In 10 pediatric asthma adherence studies using objective measures, levels of adherence ranged from a low of 19% to a high of 64%, with little change over 2 decades from 1996 to 2015.⁵³ Documenting the challenges in correct inhaler use, a quantitative prospective observational study on the time and technique of inhaler use in adults with asthma ($n = 82$) and COPD ($n = 21$) was conducted.⁵⁴ The study reported that of 60 doses expected to be taken in a month, only 34 doses (57%) were taken properly. These data highlight ineffective and irregular inhaler use. The suboptimal use of controller medications for asthma despite widespread dissemination of asthma guidelines was confirmed in a study of 275 patients requiring an asthma-related hospitalization.⁵⁵ Asthma controller medication dispensing in patients in the 12 months before the hospitalization included 63.6% with <1 dispensing, 32.4% with frequent ICS/LABA dispensings, and 4% with more LABA than ICS in nonfixed combination dispensings. Two studies further highlighted the challenges to long-term adherence to ICS. Laforest et al⁵⁶ reported in a cohort of 5096 patients 6 to 16 years of age that only 25% of patients continuously used ICS over a year period. Similarly, a retrospective analysis of persistence of treatment to 2 types of ICS/LABA delivery systems of 11,774 adolescents and adults with asthma or COPD noted extremely poor adherence, ebbing to 22.9% and 10.5% in the 2 devices during 12-month follow-up.⁵⁷

Given the importance of adherence and challenges to improve adherence in asthma, we devoted a Theme Issue to Respiratory Medicine Adherence. These reviews covered diverse adherence areas including (a) details on adherence terminology, behavioral features, and methods of assessment⁵⁸; (b) the relationship of inhaled medication mode of delivery to adherence and challenges in correct inhaler use⁵⁹; (c) determinants of adherence by age spectrum, emphasizing challenges in adolescents and older adults⁶⁰; and (d) cost-effective strategies to enhance adherence to respiratory medications among health care professionals and systems.⁶¹

Also described in the Adherence theme issue was a novel Asthma Care Model with implications for both practice and research based on mapping the sequence of events from diagnosis to treatment prescriptions, drug exposure, and health outcomes.⁶² These events were then related to patient behaviors with regard to medication adherence, symptom monitoring, managing triggers, and exacerbations. The goal of the Asthma Care Model was to generate and translate research evidence to asthma care.⁶²

Several reports supported the benefits of educational programs to optimize self-management in asthma. One report demonstrated that both asthma self-management education (9 programs) and home-based interventions (17 programs) improved asthma control and reduced exacerbations and were economically sound, as most had positive returns on investment.⁶³ Consistent with these findings, an electronic asthma self-management program with a pre-post design reported significant improvements in asthma control and quality of life after 6 weeks in 44 young African American adults with uncontrolled persistent asthma.⁶⁴

Telehealth strategies that monitor patients with asthma in real time may improve asthma outcomes. One such system is the Propeller Health telemonitoring system that assesses SABA use by employing a sensor that snaps onto a metered-dose inhaler and transmits SABA use through mobile applications on a real-time basis to the patient and provider. A randomized 1-year study in 495 children and adults with asthma reported a significant but small reduction in SABA use with active versus passive monitoring (decrease of 0.41 vs 0.31 puffs per day, respectively, $P < .001$).⁶⁵ More patients with initially uncontrolled asthma achieved control in the intervention (63%) versus the routine care (49%) group ($P < .05$). However, only 56% of patients completed monitoring throughout the study, limiting the certainty of the study findings. A pre-post designed 4-month study in 40 adults with uncontrolled asthma on guideline therapy using a smartphone application with medication reminders reported significant improvements in asthma control (ACT) and spirometry.⁶⁶ Baptist et al⁶⁷ conducted a systematic review of 16 articles on the effect of technological interventions for behavioral modification, symptom monitoring, education, or decision making in minority and inner-city asthmatic children and adolescents. The technological interventions in these studies included using MPEG audio layer-3 players, text messaging, computer/Web-based systems, video games, and interactive voice response. Overall, modest improvements were observed in knowledge attainment, adherence to therapy, asthma symptoms, and quality of life, but not in asthma health care utilization.⁶⁷ Although the positive findings of these telehealth and behavioral intervention studies are encouraging, more definitive randomized clinical trials are needed.

RHINITIS AND RHINOSINUSITIS

Rhinitis and sinusitis are extremely common in the population and probably the most common problems encountered by allergy-immunology clinicians. Our challenge and opportunity is to reduce the substantial impairment of quality of life caused by these conditions. For allergic rhinitis, we employ combinations of avoidance measures, medications, and immunotherapy.

Regarding avoidance, a personal form of avoidance was studied by Kenney et al.⁶⁸ They conducted an observational open label study of a novel nasal filter, which had previously been

found to have a substantial preventative effect for seasonal allergies, in 1073 participants with seasonal allergic rhinitis. Of 834 new users, 630 reported interest in continued use of the filters, suggesting that this form of therapy was convenient and comfortable to use and may be clinically relevant for symptom management in many patients with allergic rhinitis.

One important aspect of evaluating the efficacy of medication is the determination of what constitutes clinically meaningful improvement in relevant outcome measures. Meltzer et al⁶⁹ presented anchor-based and distribution-based methods for determining a minimal clinically important difference (MCID) for the total nasal symptom score, a commonly used rhinitis study outcome measure. The resulting MCID thresholds were “validated” by their retrospective use in 3 published studies and appear to be superior to previously suggested MCID thresholds.

The effectiveness of immunotherapy for allergic rhinitis is well established. Studies published in *JACI: In Practice* this past year provided additional information regarding the safety of immunotherapy. Maloney et al⁷⁰ studied dual treatment with grass and ragweed sublingual immunotherapy (SLIT) in 102 patients. They found that the following sequence was well tolerated: (1) 2 weeks of grass in the evening, (2) 2 weeks of ragweed in the morning and grass in the evening, and (3) 2 weeks of grass and ragweed within 5 minutes of each other at a time of day chosen by the patient. Another reassuring article was a systematic review that concluded that coseasonal initiation of subcutaneous immunotherapy (SCIT) or SLIT does not increase the risk of adverse events compared with out-of-season initiation or placebo.⁷¹

Systemic reactions are one of the well-known risks of immunotherapy. In a Pro/Con review article, Fitzhugh and Bernstein⁷² debate whether epinephrine autoinjectors should be prescribed to all patients on SCIT. They conclude that there is currently insufficient clinical evidence to make a strong recommendation for or against this practice. A much more uncommon adverse effect of immunotherapy was described in a case report of Nicolau syndrome, tissue damage and necrosis associated with medication injection, in a 16-year-old girl who was receiving maintenance pollen SCIT.⁷³ Finally, a study of 126 patients evaluated sensitization to a non-native tree as a marker for sensitization to panallergens, molecules that are highly homologous across plant species.⁷⁴ They found that sensitivity to this non-native tree, likely due to its content of the panallergen profilin, was significantly associated with sensitivity to an increased number of other aeroallergens. The authors suggest that, for polysensitized patients, studies that examine the total quantity of profilin required for an immune response to immunotherapy, without overdosing profilin components, may help to increase the safety of pollen immunotherapy while retaining efficacy.⁷⁴

For rhinosinusitis, like asthma, there is a growing focus on phenotypes and matching the optimal therapy to the patient's phenotype. This was highlighted in the July/August *JACI: In Practice* theme issue devoted to phenotypes of chronic rhinosinusitis (CRS). In addition to summarizing current clinically relevant information, all of the CRC review articles in this issue identified research questions and future directions. In their review of CRS with nasal polyps, Stevens et al⁷⁵ pointed out that the pathogenesis is not clearly defined but may be multifactorial, and that this phenotype is often associated with asthma and allergic rhinitis. The mainstay of medical treatment is intranasal

and oral corticosteroids and treatment of infectious exacerbations. Nonsteroidal anti-inflammatory drug (NSAID)-exacerbated CRS, a subset of CRS with nasal polyps, was highlighted in an article by Ledford and Lockey.⁷⁶ NSAID-exacerbated CRS occurs in 5% to 10% of patients with CRS and 15% to 40% of those with nasal polyps. The disease is related to a chronic increase in leukotriene and a decrease in prostaglandin production and may be improved by aspirin desensitization followed by regular ingestion of aspirin. CRS without nasal polyps was discussed by Cho et al,⁷⁷ who indicated that this phenotype is more common than CRS with nasal polyps and identified the many predisposing conditions and factors. They stated that there are conflicting data regarding whether this condition is characterized by neutrophilia, eosinophilia, or both. Bose et al⁷⁸ discussed infectious CRS, indicating that the etiology is usually a secondary bacterial infection that commonly complicates a viral upper respiratory infection. Infectious CRS can be treated with antimicrobials, topical or oral corticosteroids, and nasal saline. Antibiotics may also have anti-inflammatory roles in CRS, as discussed in a Pro/Con review by Bachert and Hamilos.⁷⁹

Hoyt et al⁸⁰ presented a review of allergic fungal rhinosinusitis, including the clinical, pathologic, and radiologic criteria to establish the diagnosis and the role of postoperative oral corticosteroid and possibly antifungal therapy. The theme issue also contained an Images In Allergy feature⁸¹ that nicely demonstrated the radiologic features of allergic fungal sinusitis. CRS in patients with cystic fibrosis was reviewed by Hamilos,⁸² including the frequently associated more neutrophilic nasal polyps and the potential value of topical antibiotics. Naclerio and Baroody⁸³ discussed other associations with CRS, including anatomic abnormalities, cilia motility defects, allergic sensitization, immune deficiency, dental infections, gastroesophageal reflux disease, autoimmune diseases, and smoking. These authors then presented a management algorithm for CRS.⁸³ Although CRS can be differentiated into several phenotypes, these phenotypes do not specifically identify inflammatory mechanisms that would permit targeted therapy. Endotypes of CRS based on pathomechanisms would provide that information, and emerging endotypes of CRS, structured around T helper cells and their downstream events, were considered by Bachert and Akdis.⁸⁴ Finally, Cho et al⁸⁵ “put it all together” with specific guidance regarding the diagnosis, identification of phenotypes, optimal use of imaging studies, and optimal use of standard (glucocorticosteroids and antibiotics) and newer (biologic agents) therapies.

Two other articles published in the past year provided new information regarding CRS and nasal polyps. Mahdavinia et al²⁹ published a retrospective cohort study of 1344 patients with a diagnosis of chronic rhinosinusitis. These authors demonstrated that African Americans had more severe disease and more frequent nasal polyposis, AERD, and asthma hospitalizations. As noted above, a retrospective review of 194 patients who had 24-hour urinary LTE4 determinations was presented by Divekar et al.³⁵ The study found elevated levels in patients with CRS with nasal polyps, even after adjusting for aspirin sensitivity.

Patients with rhinosinusitis were included in 3 other articles in the Journal this past year. An interesting case was reported by Hamada et al⁸⁶ in whom nasal exhalation of inhaled beclomethasone hydrofluoroalkane (being used for asthma) improved symptoms and radiologic manifestations of coexistent CRS. The authors suggested that the simple use of nasal exhalation of inhaled corticosteroids may have utility in simultaneously

controlling upper and lower airway inflammation in a cost-effective manner. Namazy et al⁸⁷ evaluated sinusitis during pregnancy in a large retrospective database cohort. In contrast to a prior report, they found that pregnant women were less likely to receive antibiotics for upper respiratory infections in general and for sinusitis specifically during pregnancy compared with the years before or after pregnancy. Maternal asthma, chronic rhinitis, and chronic sinusitis before pregnancy were risk factors for gestational antibiotic use. Finally, a review of pediatric sleep apnea syndrome pointed out that allergic rhinitis, nonallergic rhinitis, and infectious rhinosinusitis are risk factors for the condition.⁸⁸

FOOD ALLERGY AND ANAPHYLAXIS

A series of studies addressed food allergy and anaphylaxis epidemiology and risk factors, topics important for research and clinical care. Regarding anaphylaxis epidemiology, Lee et al⁸⁹ used Olmsted County, Minnesota records to determine epinephrine autoinjector prescribing patterns over 2004-2010, noting an annual increase in prescriptions of 8% per patient per year, but the rate of first-time prescriptions was stable. The increase might reflect increasing public awareness, diagnosis, or increased disease. McGowan et al⁹⁰ investigated time trends of the prevalence of sensitization to food allergens. They utilized results of serum food-specific IgE antibody levels in 6 to 19 year olds collected during the National Health and Nutrition Examination Surveys in 1988-1994 and 2005-2006 to compare sensitization rates over a decade. They included 7896 participants and measured results for milk, egg, peanut, and shrimp, considering a level ≥ 0.35 kU/L as sensitized. Surprisingly, despite many studies suggesting an increase in prevalence of food allergy, there were no significant changes in the prevalence of sensitization to milk, egg, or peanut, and sensitization to shrimp decreased markedly. Overall, sensitization was 11.2% in 1988-1994 compared with 6.1% in 2005-2006. How can sensitization rates decrease while prevalence rates of food allergy appear to have increased? A simple explanation would be improved diagnosis and recognition. However, if one accepts that sensitization is not equivalent to clinical allergy, as will be discussed further below, a more interesting explanation regards behaviors associated with diet and additional environmental influences that may promote clinical allergy among those who are sensitized. For example, delayed introduction of peanut, possibly a factor in the later survey, could convert a sensitized state into clinical allergy. This interesting study also suggests different outcomes based on race and ethnicity, underscoring the complex interactions of genetics, environment, and immune response.

A study by Chang et al⁹¹ also elucidated a phenomenon related to clinical outcomes of food allergy among those sensitized as it relates to ingestion exposure to foods. They evaluated outcomes of immediate allergic reactions to foods that had been removed from the diet of children with atopic dermatitis for management of the rash. Their study was a chart review of 298 patients, and they found that 19% of the sensitized children without a previous history of immediate reactions developed new immediate food reactions after undergoing the elimination diet. Thirty percent of these reactions included anaphylaxis. From a clinical perspective, this observation underscores the risk that treatment of atopic dermatitis by food elimination may result in new serious food allergies, which should be considered during management. It also provides supporting evidence to the

hypothesis, described earlier, that alteration in eating habits may play a role in whether sensitization manifests as clinical reactivity. Indeed, atopic dermatitis care should be comprehensive, addressing not only allergen triggers² but also irritants, inflammation, infection, and other aspects that can be enhanced by a collaborative approach with primary care physicians.³

The discordance between sensitization and clinical allergy was also underscored in a study by Gupta et al,⁹² who evaluated the risk of food sensitization and allergy for siblings of a proband with food allergy. They evaluated 1120 food-allergic children with at least one sibling, noting that 66.6% of the siblings were food sensitized but only 13.6% were clinically reactive. The clinical message from this study is that screening tests performed on siblings of a food-allergic child should be discouraged or undertaken with caution because of a high likelihood of detecting clinically irrelevant sensitization in children who are only at modestly higher risk than the general population.

Several studies published this year provided insight on the clinical characteristics of food allergies, scenarios to watch out for in practice. McWilliam et al⁹³ described a series of 38 infants with diarrhea, vomiting, abdominal distention, and irritability brought on by a variety of foods and treatable primarily only with an amino acid-based formula. Many of these infants could only ingest several foods successfully, and most showed no signs of sensitization, while several had coexisting food protein-induced enterocolitis syndrome (FPIES). The authors noted that growth was normal over several years of follow-up, but most of the children continued to require significant dietary restriction. The authors suspected a global problem with oral tolerance development in these infants and encouraged more study of this difficult problem. Gleich et al⁹⁴ described 8 adults with food allergy to shrimp where the patients generally had no evidence of IgE sensitization but experienced symptoms typical of FPIES, a diagnosis as noted above that usually is confined to infants and young children. These adults experienced abdominal pain and vomiting in the absence of skin or respiratory symptoms, approximately 2 hours after ingestion of shrimp. Roenneberg et al⁹⁵ described a case of particularly severe delayed anaphylaxis to meat attributed to galactose- α -1,3-galactose (α -gal) in a patient with indolent mastocytosis, suggesting that the underlying disease may have enhanced reactivity and emphasizing the need to consider unusual triggers of reactions in persons with mastocytosis. Although tick bites are the presumed primary cause of sensitization to α -gal with resulting food allergy, McGain et al⁹⁶ reminded us that tick bite allergy also exists and described 6 fatalities from this rare allergy.

Several studies focused on food allergy diagnostics and the use of component testing.^{97,98} For example, a study of hazelnut allergy highlighted clinical utility of testing for IgE to Cor a 14.⁹⁸ Ultimately, the oral food challenge (OFC) is often required for diagnosis or to identify resolution,⁹⁹ and 3 studies this year provided clinical insights regarding OFCs. Sicherer et al¹⁰⁰ used data from 512 participants in the Consortium of Food Allergy Research's observational study to address the common concern that ingestion of an allergen leading to a reaction during an OFC might boost IgE and alter the course of the allergy. However, data on egg, milk, and peanut OFCs resulting in reactions ($n = 20$ – 27 for each food) and data regarding natural exposure reactions ($n = 377$) failed to show boosting of sensitization based on serum IgE or skin test size. These results should provide some level of comfort in undertaking the OFCs. Ram et al¹⁰¹

presented data focused on 366 OFCs performed at their center to foods that are less commonly tested than milk, egg, peanut, soy, and wheat, noting that 81% of the tests were passed without symptoms, compared with this group's pass rate to more common allergens (45% pass rate). The authors used these data to encourage practitioners to perform OFCs. The risks of a reaction during OFC are well recognized, but Ogura et al¹⁰² reminded clinicians to be aware that acute pancreatitis is a rare complication.

A knowledgeable clinician should be aware of many facets of food allergy care and identification of anaphylaxis,¹⁰³ and, unfortunately, deficiencies exist even for common topics such as labeling and emergency care.^{104,105} Indeed, parents perceive several deficiencies in management from pediatricians and allergists.¹⁰⁶ Often neglected areas of care include nutrition and psychosocial aspects. Beck et al¹⁰⁷ evaluated anthropometrics in children followed in the HealthNuts study, a population-based study in Australia, and found that at age 1 year, infants with food allergy and/or eczema were smaller and lighter than infants with neither condition, and, by age 4 years, children with persistent food allergy and persistent eczema, but not those with resolved allergy, were still smaller and weighed less. Therefore, children with concurrent food allergy and eczema should be followed closely for appropriate eczema management and dietary guidance. Another important problem for individuals and families managing food allergy regards quality of life, anxiety, bullying, and other psychosocial concerns.^{108,109} A review article by Herbert et al¹⁰⁹ provides practical advice on identifying, managing, and referring children and families for appropriate management of this important aspect of food allergy.

With the apparent increase in food allergy, identification of risk factors that may lead to prevention strategies has become a primary focus. Cutaneous sensitization is one potential potent risk factor, and Radhakrishna et al¹¹⁰ provided a compelling example that this phenomenon can occur in adults. They described a 30-year-old woman who became sensitized to oat through an oat-containing skin care product and subsequently had anaphylaxis to ingested oat. Childhood vaccination is another target for consideration of food allergy risk, with one theory being that a switch from cellular to acellular pertussis might have skewed toward an allergic immune response. However, Venter et al¹¹¹ did not identify an increase in food allergy or atopy in evaluation of a cohort of 819 children receiving one or the other type of vaccine around the same time almost randomly based on availability. Allen and Koplin¹¹² provide a comprehensive review that describes the latest theories regarding alterable risks for the development of food allergy, including inflamed skin as a pathway for sensitization, environmental exposures, the microbiota, and dietary factors including vitamin D. They describe the early introduction of allergenic foods as a potential prevention strategy, which has been of highest focus recently. A study by Onizawa et al,¹¹³ for example, used a case-control approach comparing patients with IgE mediated cow's milk allergy to controls to evaluate the timing of introduction of milk on outcomes of milk allergy. The adjusted OR of delayed or no regular ingestion of cow's milk comparing those with cow's milk allergy to controls with egg allergy was 10.2 (95% CI, 2.5–41.6), giving another example that early introduction may be associated with lower incidence of allergy. Thus far, the evidence of the preventative benefit of early introduction of allergens is greatest for peanut, but adding an allergen such as peanut to the diet early

can be complicated. Greenhawt et al¹¹⁴ provide a helpful review describing the complexities of undertaking this intervention.

DRUG ALLERGY

Drug allergy is a common and important clinical problem. It is also a subject that frequently puts allergy-immunology clinicians in direct contact with other medical practitioners. Furthermore, as knowledge and specific testing and treatment protocols increase, drug allergy is a potential target for expansion of the role of the allergist/immunologist. Indeed, the theme of the 2017 American Academy of Asthma, Allergy and Immunology (AAAAI) Annual Meeting is "Expanding Practice: Diagnosis and Treatment of Drug Allergy." Articles published in *JACI: In Practice* in 2016 explored the epidemiology, etiology, diagnosis, and management, especially with desensitization, of drug allergy.

Three articles provided new information regarding the epidemiology of drug allergy. In a review of 1634 charts randomly selected from patients treated in their teaching hospital emergency department, Saff et al¹¹⁵ reported that most reactions occurred to antibiotics (42%) followed by intravenous contrast (7%) and NSAIDs (6%). The authors also concluded that specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and E codes could be used to identify allergic drug reactions. The consequences of carrying a diagnosis of drug allergy were highlighted in a prospective Dutch matched cohort study of hospitalized patients that showed that patients labeled as penicillin allergic had higher risks of receiving reserve antibiotics and of being re-hospitalized within 12 weeks.¹¹⁶ Finally, Trubiano et al¹¹⁷ examined the differences in the characteristics of delayed cutaneous adverse drug reactions in hospitalized patients between antibiotic-associated and nonantibiotic-associated reactions. They observed that, compared with nonantibiotic reactions, antibiotic-associated reactions were associated with a higher prevalence of drug reaction with eosinophilia and systemic symptoms (DRESS), longer length of stay, higher Charlson comorbidity index, shorter latency between commencement of exposure and reaction, and increased inpatient mortality. Sulfonamide antibiotics and glycopeptides (vancomycin and teicoplanin) were implicated in 20% of the antibiotic-associated reactions.

Some articles published in 2016 provided new insights into the etiologies of adverse drug reactions. Two articles highlighted the potential selective nature of NSAID reactions. One report presented a patient with a serum sickness reaction to naproxen who was able to tolerate aspirin and ibuprofen.¹¹⁸ Another article described a patient who tolerated aspirin (and ibuprofen) but reacted to both paracetamol and celecoxib and had a positive intradermal skin test to dipyrene.¹¹⁹ On the other hand, 2 studies demonstrated cross-reactivity among local anesthetic reactions. Lorenzini et al¹²⁰ described a patient with delayed hypersensitivity reactions to several local anesthetics, all of which contained a meta-xylene entity. However, the patient tolerated articaine, which is a thiophene derivative. The other case report presented a patient with delayed cutaneous allergic reactions to lidocaine, mepivacaine, and bupivacaine.¹²¹ The patient refused additional testing so articaine was not tried.

Antibiotics are common causes of adverse drug reactions, and three 2016 *In Practice* articles provided new insights into these reactions. Of concern was a report of 96 patients treated with ceftaroline, in whom 31 adverse drug reactions in 20 (21%) patients were observed.¹²² The authors and an accompanying

Editorial¹²³ expressed concern over the frequency of adverse reactions observed in postmarketing use compared with premarketing clinical trials and conclude that more data are needed to understand the frequency and predictors of ceftaroline adverse drug reactions. Uytendaele et al¹²⁴ studied 66 patients with hypersensitivity to another cephalosporin, cefazolin. A clinically important observation was that the data confirmed that cefazolin hypersensitivity appears to be a selective allergy with good tolerance to other β -lactam antibiotics. An unusual case of drug fever after a single dose of amoxicillin/clavulanate was presented by Mori et al.¹²⁵ Hapten-specific T-cell involvement with TNF- α production pathogenesis was suggested by *in vitro* tests.

Several studies provided useful information regarding perioperative drug reactions. Kuhlen et al¹²⁶ described their evaluations of 25 patients with perioperative hypersensitivity reactions. The most common agent identified was cefazolin. Subsequent anesthesia was tolerated in 7 of 8 patients undergoing the reported comprehensive evaluation and management plan. Latex is a known cause of reactions at the time of surgery, but in 3 patients with intraoperative anaphylaxis to latex, the reactions were possibly facilitated by the administration of oxytocin and vasopressin.¹²⁷ A unique sensitizing exposure was described in a case of anaphylaxis to intravenous gentamycin during surgery in which the sensitization was suspected to be through gentamicin-loaded bone cement.¹²⁸ Finally, Spoerl et al¹²⁹ presented 3 cases with chlorhexidine allergy (2 of which were perioperative and 1 was during an intrauterine device insertion), with the value of specific IgE against chlorhexidine and safe performance of skin tests discussed (see below).

Severe cutaneous adverse drug reactions, each with unique aspects, were the subjects of 4 *JACI: In Practice* articles this past year. In one article, a typical DRESS was described due to diindolylmethane, a dietary supplement and potential investigational drug.¹³⁰ In another article, a case of DRESS associated with allopurinol was reported with the unusual manifestation of acute necrotizing eosinophilic myocarditis and death due to papillary muscle rupture.¹³¹ Tremblay et al¹³² reported the first case of toxic epidermal necrolysis in a patient with cystic fibrosis who received multiple antimicrobials within 4 weeks before the reaction. The authors speculated that ciprofloxacin or meropenem were most likely, although the exact etiology could not be confirmed due to lack of sensitive or reproducible skin or *in vitro* tests for confirmation of toxic epidermal necrolysis. Finally, this past year featured an interesting case report of a patient with acute generalized exanthematous pustulosis due to diltiazem.¹³³ Positive patch tests to diltiazem and verapamil but negative to nifedipine were demonstrated, suggesting that nifedipine did not cross-react with the other 2 calcium channel blockers and might have been tolerated, although this was not tested in this patient.

This past year's *JACI: In Practice* issues also included descriptions of adverse drug reactions to less commonly recognized triggers, all confirmed by skin tests. One patient demonstrated hypersensitivity to ferrous but tolerance of ferric iron salts, with positive skin tests to ferrous but not ferric preparations observed.¹³⁴ A case series described 5 patients with anaphylaxis induced by proton-pump inhibitors. Positive skin tests were documented to the culprit drug in all patients.¹³⁵ A patient with bullous nonpigmenting multifocal fixed drug eruption due to pseudoephedrine was described, confirmed by a positive patch test with the culprit drug on the previously affected area.¹³⁶ Four patients were described with immediate hypersensitivity to Cidex

TABLE I. Examples of 2016 advances and observations from *JACI: In Practice*

Clinical area	Advances and observations
Pediatric asthma	- Study findings from the NIH clinical trial networks provided the most robust evidence for guideline recommendations for controller treatment of pediatric asthma across the age spectrum¹¹⁻¹⁵ - Mouse sensitization was an independent risk factor for rhinitis in adolescents and children with asthma¹⁶ - School-based interactive learning and observed medication use improved adherence and management among adolescents¹⁷ - Health-related quality of life was markedly impaired in adolescents with uncontrolled asthma¹⁸ - Marked variability exists in quality of asthma care among primary care practices,¹⁹ and misunderstandings exist in medication use directions between family and physicians²⁰ that affect asthma burden in children. - AERD must be considered in children, though less common than in adults²¹ - Modifiable risk factors for asthma during childhood were identified: prenatal (obesity and weight gain), perinatal (Caesarian births), and postnatal (severe RSV infection, obesity, indoor mold exposure and outdoor air pollution)²² - Obesity in children contributed to increases in mechanical ventilation and costs of asthma hospitalizations²³
Adult asthma	- Two useful questionnaires to monitor asthma control were validated: the Asthma Symptom Diary²⁴ and the Pregnancy Asthma Control Test²⁵ - Lung sound analysis was reported as a useful noninvasive, simple and reproducible technique that was related to airway inflammation and bronchial hyperresponsiveness²⁶ - Risk factors for more burdensome asthma in adults were reported: female sex,³⁰ depression,²⁷ hypertension,²⁸ chronic rhinosinusitis in African Americans,²⁹ homozygosity of the Arg/Arg polymorphism,³² and COPD disease coding³⁴ - Corticosteroid pharmacokinetic abnormalities were demonstrated in the obese and overweight patient with corticosteroid-resistant asthma³¹ 24-h LTE4 levels were predictive for challenge-confirmed aspirin sensitivity³⁵ - Severe uncontrolled asthma was identified in 2.3% of adolescents and adults with persistent asthma and was associated with higher health care utilization and cost³³ - Active asthma in adults was associated with incident myocardial infarction³⁶ - Clinically meaningful variations in total serum IgE levels were seen during a year observation which could affect both the eligibility for and dose of omalizumab, an anti-IgE biological³⁷ - Monitoring total serum IgE levels in patients with ABPA receiving omalizumab could help to identify exacerbations³⁹ and response to therapy⁴⁰ - Comprehensive household allergen avoidance program was successful in reducing allergen levels, but not the step-care level of controller medication⁴³ - Tiotropium, a long-acting anticholinergic, showed bronchodilator efficacy and safety in adults uncontrolled on low- to medium-dose ICS⁴⁴ - Given the importance of mold/fungal exposure in asthma causation and progression, several reviews to increase mold allergy knowledge and clinical skills were published⁴⁷⁻⁵²
Adherence and self-management	- Adherence to asthma controllers is suboptimal: long-term controller medication use in 10 pediatric adherence trials ranged from a low of 19% to high of 64%,⁵³ only 57% of doses of inhaled medications were taken correctly,⁵⁴ and only 25% used inhaled ICS over a year period⁵⁶ - Educational programs^{63,64} and telehealth strategies⁶⁵⁻⁶⁷ were reported to optimize self-management and improve asthma outcomes. - Strategies to recognize and improve poor adherence exist, are clinically useful, and were reviewed in several publications⁵⁸⁻⁶²
Rhinitis	- A novel nasal filter was found to be convenient and comfortable to use and may be clinically relevant for symptom management in many patients with allergic rhinitis⁶⁸ - Minimal clinically important difference thresholds were validated for the TNSS⁶⁹ - A protocol for initiating dual treatment with grass and ragweed SLIT was well-tolerated⁷⁰ - A systematic review concluded that coseasonal initiation of SCIT or SLIT does not increase the risk of adverse events compared with out-of-season initiation or placebo⁷¹ - A case of Nicolau syndrome (tissue damage and necrosis associated with medication injection) was reported in a patient who was receiving maintenance pollen SCIT⁷³ - Sensitization to a non-native tree as a marker for sensitization to panallergens such as profilin was significantly associated with sensitivity to an increased number of other aeroallergens⁷⁴
Chronic rhinosinusitis (CRS)	- Sinusitis phenotypes were reviewed, including CRS with nasal polyps,⁷⁵ NSAID-exacerbated CRS,⁷⁶ CRS without nasal polyps,⁷⁷ infectious CRS,⁷⁸ allergic fungal rhinosinusitis,⁸⁰ CRS in patients with cystic fibrosis,⁸² and other phenotypes⁸³ - Endotypes of CRS based on pathomechanisms, structured around T helper cells and their downstream events, were discussed⁸⁴ - Antibiotics may have anti-inflammatory roles in CRS⁷⁹

(continued)

TABLE I. (Continued)

Clinical area	Advances and observations
	• Management algorithms based on phenotypes were presented^{83,85} • African Americans with CRS have more severe disease, more frequent nasal polyposis, more frequent AERD, and increased asthma hospitalizations²⁹ • Elevated 24-h urinary LTE4 levels were found in patients with CRS with nasal polyps, even after adjusting for aspirin sensitivity³⁵ • Nasal exhalation of an ICS being used for asthma improved symptoms and radiologic manifestations of coexistent CRS⁸⁶ • Pregnant women were less likely to receive antibiotics for sinusitis during pregnancy compared with the years before or after pregnancy⁸⁷ • A review of pediatric sleep apnea syndrome pointed out that allergic rhinitis, nonallergic rhinitis, and infectious rhinosinusitis are risk factors for the condition⁸⁸
Food allergy and anaphylaxis	• Increase in food allergy prevalence without an increase in food allergy sensitization suggests alternative explanations for emergence of disease⁹⁰ • Removing a tolerated food to treat atopic dermatitis can result in development of new anaphylactic allergy to that food⁹¹ • Siblings of a child with food allergy are at small increased risk of food allergy but high increased risk of innocent sensitization, underscoring caution regarding screening tests⁹² • Adults may have FPIES to shellfish⁹⁴ • Description of a syndrome of multiple food allergy/intolerance⁹³ • Studies on component testing for food allergy diagnostics^{97,98} • Allergic reactions to egg, milk, or peanut during OFC or accidental ingestion did not “boost” sensitization¹⁰⁰ • OFCs should be encouraged for nonmajor food allergens as these are uncommonly confirmed allergies¹⁰¹ • Children with food allergy and eczema should be monitored closely for nutrition/growth¹⁰⁷ • A case control study of cow’s milk allergy added further evidence that delayed allergen exposure is associated with allergy development¹¹³ • A cohort study suggested that the switch from whole to acellular pertussis in vaccines did not result in more food allergy/atopy¹¹¹
Drug allergy	• Most drug reactions presenting to the ED occurred to antibiotics (42%) followed by intravenous contrast (7%) and NSAID (6%)¹¹⁵ • Hospitalized patients labeled as penicillin allergic had higher risks of receiving reserve antibiotics and of being rehospitalized within 12 wk¹¹⁶ • Compared with delayed cutaneous nonantibiotic reactions in hospitalized patients, antibiotic-associated reactions were associated with a higher prevalence of DRESS, longer length of stay, and increased inpatient mortality¹¹⁷ • NSAID reactions may be selective: a patient with a serum sickness reaction to naproxen was able to tolerate aspirin and ibuprofen,¹¹⁸ and a patient who tolerated aspirin (and ibuprofen) reacted to paracetamol and celecoxib¹¹⁹ • Two patients reacted to several amide local anesthetics,^{120,121} which may be due their meta-xylene entity, not contained in articaine¹²⁰ • A high frequency of adverse drug reactions to ceftaroline was reported¹²² • Regarding perioperative drug reactions, the most common etiologic agent identified was cefazolin¹²⁶; reactions to latex may be facilitated by the administration of oxytocin and vasopressin¹²⁷; and reactions to intravenous gentamycin¹²⁸ and chlorhexidine¹²⁹ were reported • Unique cases of severe cutaneous adverse drug reactions were reported: DRESS due to diindolylmethane¹³⁰; DRESS associated with allopurinol with acute necrotizing eosinophilic myocarditis and death due to papillary muscle rupture¹³¹; TEN in a patient with CF¹³²; and acute generalized exanthematous pustulosis due to diltiazem¹³³ • Based on history, predictors of a final diagnosis of drug allergy included beta-lactam drug class, time to reaction less than 1 h, clinical presentation suggestive of allergic disease, and shorter time from reaction to medical consultation¹³⁹ • Positive skin tests were documented and felt to be meaningful for a number of drugs associated with hypersensitivity (Table II). In contrast, a substantial number of false positives skin tests were found for clarithromycin¹⁴² • Regarding <i>in vitro</i> tests, the BAT was reported to be useful for evaluation of hypersensitivity to pertuzamab,¹⁴³ etoricoxib,¹⁴⁴ and cefazolin,¹⁴⁵ and specific IgE was demonstrated in patients with chlorhexidine allergy¹²⁹ and immediate hypersensitivity to Cidex¹³⁷ • A number of successful drug desensitization protocols were described (Table III). One unsuccessful desensitization to rifampicin was also reported¹⁵⁵
Urticaria and angioedema	• Description of the features of patients with cholinergic urticaria with anaphylaxis, suggesting that cholinergic triggers should be considered in investigation of anaphylaxis¹⁵⁶

(continued)

TABLE I. (Continued)

Clinical area	Advances and observations
	• Omalizumab was effective for aquagenic urticaria¹⁵⁸ • Basophil activation may be a marker for omalizumab response in CU¹⁵⁷ • Validation of a quality of life instrument for HAE¹⁶⁰ • Characterization of efficacy, tolerability, and safety of alkylated androgens for HAE¹⁶¹ • Data suggesting safety of home therapy with C1-inhibitor concentrate for HAE¹⁶²
Eosinophilic disorders	• A variety of carrier vehicles can be used to administer topical steroid (off-label use) for EoE¹⁶⁶ • Children with HES have similar treatment response and prognosis to adults, and adult algorithms may be applicable¹⁶⁸
Immunodeficiency	• In patients with persistent unexplained hypereosinophilia, primary immunodeficiency was found significantly more commonly in children than adults¹⁶⁸ • Precision medicine helped to identify genetic variants of combined immunodeficiency disease and other immunodeficiency disorders^{169,170,175} • Inhaled fluticasone propionate was successful in treating IgG4-related pulmonary disease¹⁷¹ • Use of enteral immunoglobulin eradicated persistent norovirus in NEMO syndrome¹⁷² • Patients with CHARGE syndrome appeared not to manifest immunodeficiency¹⁷⁶ • A proposed new definition of CVID that excluded patients with T-cell defects improved the accuracy of CVID diagnosis¹⁷⁷ • A new questionnaire to assess the impact of CVID on patients was developed and validated¹⁷⁸ • The "International Consensus Document (ICON): common variable immunodeficiency disorders" based on critical literature review was reported¹⁷⁹ • The array of immunodeficiency disorders was reviewed with emphasis on recognition, diagnosis, and management¹⁸⁰⁻¹⁸⁷

ABPA, Allergic bronchopulmonary aspergillosis; AERD, aspirin-exacerbated respiratory disease; BAT, basophil activation test; CF, cystic fibrosis; CHARGE, coloboma, heart disease, choanal atresia, growth/mental retardation, genitourinary malformations, ear abnormalities; COPD, chronic obstructive pulmonary disease; CU, chronic urticaria; CVID, common variable immune deficiency; DRESS, drug reaction with eosinophilia and systemic symptoms; ED, emergency department; EoE, eosinophilic esophagitis; FPIES, food protein-induced enterocolitis syndrome; HAE, hereditary angioedema; HES, hypereosinophilic syndromes; ICS, inhaled corticosteroids; LTE4, leukotriene E4; NIH, National Institutes of Health; NSAID, nonsteroidal anti-inflammatory drug; OFC, oral food challenge; RSV, respiratory syncytial virus; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; TEN, toxic epidermal necrolysis; TNSS, total nasal symptom score.

OPA, which was used to disinfect fibrolaryngoscopes employed for repeated fibrolaryngoscopy surveillance after surgery for neoplasia.¹³⁷ Prick skin tests were positive in all patients, and *in vitro* tests were positive in 3 of the 4. Finally, Foer et al¹³⁸ reviewed 24 cases of progesterone hypersensitivity. Based on this large case series, a new classification was proposed (endogenous versus exogenous). These authors also provided information regarding progesterone testing and desensitization (see below).

An important goal in the field of drug allergy is to make the diagnosis of an adverse drug reaction and to identify the responsible drug. Santurino et al¹³⁹ developed a mathematical model to use a drug reaction history to predict the likelihood of a diagnosis of an allergic drug reaction after evaluation. Predictors of a final diagnosis of drug allergy included older age, male sex, beta-lactam drug class, only one drug involved, time to reaction less than 1 hour, clinical presentation suggestive of allergic disease, and shorter time from reaction to medical consultation.¹³⁹

The gold standard for the diagnosis of an adverse drug reaction is a positive drug challenge. However, due to the discomfort and potential severe reactions associated with positive challenges, skin testing and *in vitro* testing have been studied in the evaluation of drug allergy as a means of obviating the need for drug challenge. Immediate and delayed skin testing have been found to be useful in the evaluation of several drug reactions described over the past year in *JACI: In Practice* (Table II). Penicillin skin testing is the most common and well-studied drug skin testing procedure, but 2 cautionary reports appeared this past year. One was a case report of a severe delayed skin reaction (blisters and bullae) after intradermal testing with ampicillin/amoxicillin,¹⁴⁰

and the other was a case report of resensitization to amoxicillin induced by intradermal testing and oral challenge resulting in anaphylaxis on subsequent exposure.¹⁴¹ Although it is important to note the potential for these reactions, these adverse consequences are considered rare enough so as not to discourage skin testing and challenge in the evaluation of patients with a history of penicillin allergy.

A key issue in the use of drug skin testing is the determination of the optimal (nonirritating) concentration. Cavkaytar et al¹⁴² studied clarithromycin skin tests in 45 children with a history of suspected hypersensitivity to clarithromycin and found a substantial number of false positives, even using more dilute solutions than used in prior studies. The authors recommended challenge without skin tests in children with histories of mild mucocutaneous reactions to clarithromycin. In contrast, in a study mentioned above of 66 patients with a history of perioperative anaphylaxis and cefazolin exposure, the authors reported that increasing the cefazolin concentration for skin testing up to 20 mg/mL benefited the sensitivity of the diagnostic technique.¹²⁴ They also confirmed that this was not an irritating concentration in the 30 cefazolin-exposed individuals in whom an alternate etiology for their perioperative anaphylaxis was identified.

Regarding *in vitro* tests, 3 papers this past year supported the value of the basophil activation test for evaluation of hypersensitivity to pertuzumab (a monoclonal antibody for breast cancer),¹⁴³ etoricoxib (a COX-2 inhibitor),¹⁴⁴ and cefazolin.¹⁴⁵ There was also a report cited above of a patient with allergic reactions to lidocaine, mepivacaine, and bupivacaine that

TABLE II. Features of 2016 *JACI: In Practice* reports of the use of skin tests in the diagnosis of drug allergy

Reference	Drug	No. of patients studied	Clinical manifestations of reactions (No. of patients)	Type of test; concentrations positive (No. of patients)	Comments
124	Cefazolin	66	Perioperative anaphylaxis	ID; 2 mg/mL (12)	20 mg/mL not irritating in 30 controls
129	Chlorhexidine 0.5%	3	Anaphylaxis	ID; 20 mg/mL (7) ID; 1:10,000 (1) Pr; 1:1 and ID; 1:100,000 (1)	
137	Cidex 0.55%	4	Anaphylaxis (1), U/A (3)	Pr; 1:1 (4)	1:1 not irritating in 5 nonatopic controls
188	Docetaxel	1	Erythrodysesthesia-like skin eruption	ID; 0.1 and 1 mg/mL	Test became positive at day 6
134	Ferrous (II) glycine sulfate	1	U	ID; 1:10	
135	Protein pump inhibitors (40 mg/mL)	5	Anaphylaxis	Responsible drugs: Pr; undiluted (2) ID; 1:100 (1) ID; 1:10 (2)	
189	Pristinamycin 50 mg/mL	64	Anaphylaxis (10), U/A (28), MPE (14), AGEP (3), Other (9)	Pr; undiluted (4/10) PT; 10% (4/13)	No skin testing in 41 patients
138	Progesterone 50 mg/mL	24	Anaphylaxis (2), Asthma (3), U/A (13), Dermatitis (13)	Pr; undiluted ID; 1:10,000, 1:1000, 1:100 12 positive (dilutions of positive tests not reported)	Patients may have had more than one type of clinical manifestation; either benzyl alcohol or olive oil used as skin test diluent
136	Pseudoephedrine	1	Bullous nonpigmenting multifocal FDE	PT; 10% in DMSO	Positive on lesional but not nonlesional skin

AGEP, Acute generalized exanthematous pustulosis; A, angioedema; DMSO, dimethyl sulfoxide; FDE, fixed drug eruption; ID, intradermal; MPE, maculopapular exanthema; Pr, prick test; PT, patch test; U, urticaria.

described an *in vitro* positive test involving measurement of eosinophil cationic protein levels after the incubation of whole blood with the suspected drugs.¹²¹ In addition, as noted above, 3 cases of chlorhexidine allergy with positive specific IgE against chlorhexidine¹²⁹ and 4 patients with immediate hypersensitivity to Cidex in whom specific-IgE was demonstrated in three¹³⁷ were described.

The management of proven or highly suspected drug allergy is generally avoidance of that drug and other structurally similar medications. However, there are circumstances in which such a drug is essential and avoidance entails substantial risk. In this case, drug desensitization, one of the most valuable skills of the allergist-immunologist, may be considered. *JACI: In Practice* showcased many desensitization protocols in 2016 (Table III). Sloane et al¹⁴⁶ presented a large series of 2177 rapid drug desensitization (RDD) procedures to chemotherapy drugs and monoclonal antibodies in 370 patients with cancer, vasculitis, hematological conditions, and connective tissue diseases. RDD allowed all patients to receive safely the full dose of the medication to which they were reactive. In addition, a shorter protocol for RDD to carboplatin and taxanes was

published.¹⁴⁷ Case reports or case series described successful desensitization protocols for a number of other products.^{138,143,148-154} Table II summarizes the number of procedures, patients, and characteristics of the desensitization protocols described in these reports. Unfortunately, one unsuccessful attempt at desensitization to rifampicin was reported,¹⁵⁵ with anaphylaxis occurring during the rapid oral procedure and the patient refusing further modified attempts at desensitization.

URTICARIA AND ANGIOEDEMA

Cholinergic urticaria is a common form of urticaria triggered by heat, exercise, and emotion. Vadas et al¹⁵⁶ described 19 patients with anaphylaxis along with cholinergic urticaria from these triggers. The affected patients were primarily females (79%) with a mean age of onset at age 28 years. The patients had a mean of 9.41 episodes per year, and the common triggers of anaphylaxis were high temperatures (100%), exertion (90%), and stress (79%). Symptoms included cholinergic urticaria (95%), upper (79%) and lower (79%)

TABLE III. Features of desensitization protocols published in *JACI: In Practice* in 2016

Reference	Drug	No. of procedures/ patients	Route/type	No. of solutions/steps	Premedication
146	Chemotherapy and monoclonal antibodies	2177/370	IV/rapid	1-4/12-16	Variable, based on the patient's symptoms during the initial reaction
147	Carboplatin and taxanes	58/12	IV/rapid	1/16	Aspirin, montelukast, dexamethasone, dexchlorpheniramine, ranitidine
148	Deferasirox	1/1	Oral/slow	—	Cetirizine
149	Lysosomal disease enzyme replacement	4/4	IV/rapid	3/12	Not described
150	Melphalan	1/1	IV/rapid	5/17	Cetirizine, montelukast, aspirin, diphenhydramine, famotidine, dexamethasone, ondansetron
143	Pertuzumab	1/1	IV/rapid	4/16	Montelukast, aspirin, dexamethasone, cetirizine
138	Progestogen	3/3	IM/rapid	1/6	H1 and H2 blockers
		8/8	Oral/slow	—	None
151	Rituximab	53/7	IV/rapid	3/12	Prednisone, montelukast, promethazine, desloratadine, ranitidine, and acetaminophen
152	Sirolimus	1/1	Oral/rapid	3/7	None
153	Temozolomide	16/14	Oral/rapid	3/14	None
154	Von Willebrand factor products	2/2	IV/rapid	3/12	Diphenhydramine

IV, Intravenous.

airway symptoms, gastrointestinal involvement (58%), and cardiovascular manifestations (79%). Baseline tryptase levels were normal in all but one patient. The authors suggested that cholinergic triggers should be considered in the investigation of anaphylaxis.

Treatment of urticaria was a focus of 3 reports. Palacios et al¹⁵⁷ performed a retrospective study of 41 adults with chronic urticaria (CU) treated with omalizumab, noting a 71% response rate. They used a basophil CD203c assay (serum of patients with CU is used to test activation of donor basophils measured by upregulation of CD203c) as a biomarker of response to treatment and found that a negative result for upregulating activity carried an OR of 6.7 (95% CI, 1.4-31) for response. Although this test, if validated, may be a means to predict response, this finding was unexpected because upregulating activity is thought to reflect autoantibodies to IgE or the IgE receptor and yet upregulation was associated with less likely clinical response. The authors suggest that alternative mechanisms may be responsible for the observation. In another report regarding omalizumab, Rorie and Gierer¹⁵⁸ noted treatment efficacy of omalizumab in a case of aquagenic urticaria, a rare disorder not expected to involve IgE.

Another difficult aspect of CU care is for those experiencing exacerbations from use of NSAIDs. Trautmann et al¹⁵⁹ used H₁-antihistamine premedication (desloratadine, 5 mg orally) 30 minutes before NSAID challenge in 21 patients with NSAID-induced or exacerbated urticaria. In a retrospective review, 17 of 21 patients tolerated 16 single dose provocations with a strong cyclooxygenase inhibiting NSAID and 2 provocations with weak ones, indicating that a majority pretreated were tolerant. The study is limited by factors including a retrospective design, possible selection issues, a lack of challenge confirmed NSAID-induced urticaria for the majority tested, and lack of long-term data after repeated NSAID doses. Nonetheless, these

observations suggest a potentially effective and practical approach worthy of additional study.

Several studies published in the Journal in 2016 addressed assessment and management of hereditary angioedema (HAE). HAE has a strong impact on quality of life, and experts suggest using this measure for assessing management.¹⁶⁰ Prior et al¹⁶⁰ performed a field study of an instrument to measure quality of life in HAE; the study, involving 18 countries, showed good reliability and validity. Regarding treatment, Alkylated androgens (AA) have been widely used for prophylaxis. Zuraw et al¹⁶¹ looked at the tolerability and safety of AAs for HAE. They performed a retrospective cross-sectional questionnaire study (n = 650) with a Web-based survey. They included 344 current, 180 past, and 126 never-users of AA. They found that AA decreased attack frequency and severity in previous ($P < .001$) and current AA users ($P < .001$). However, they noted variability in the effectiveness. Those who discontinued AA reported significantly less benefit. Most users reported frequent side effects that were dose-related and often severe. With the advent of new therapies, the authors suggest not using AA for most patients, and, if used, trialing the lowest possible dose.

Regarding other treatment modalities, Riedl et al¹⁶² presented data to describe safety and usage patterns from a large (343 patient) multicenter registry of users of nanofiltered C1-inhibitor concentrate (Berinert; "pnfC1-INH"), which is approved in the United States for treating HAE attacks and in many European countries for attack treatment and short-term prophylaxis. The study included 30 US and 7 European sites. There were 11,848 infusions for attacks and 3,142 infusions for prophylaxis. Approximately 95% of infusions were administered outside of a health care setting. No adverse events were reported pre-enrollment. Post-enrollment (n = 296 subjects; 9,148 infusions), 252 adverse events were reported in 85 (28.7%) subjects, and 9 events were considered related to pnfC1-INH.

Two thromboembolic events were reported in subjects with thrombotic risk factors. The authors concluded that the data showed a high level of safety regardless of administration setting or reason for use. In another report,¹⁶³ 2 patients with acquired C1 inhibitor deficiency, responsive to icatibant, were evaluated for underlying triggers and diagnosed with B-cell lymphoproliferative disease. The patients showed improvement with rituximab, and the authors highlight the importance of evaluating such patients for underlying malignancy and the potential efficacy of rituximab for treatment.

EOSINOPHILIC DISORDERS

Eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis present difficult diagnostic and treatment challenges.¹⁶⁴ Although these disorders are triggered by food allergens, the role of IgE is debated. Chen et al¹⁶⁵ presented a case of eosinophilic esophagitis in a patient with common variable immunodeficiency, with profoundly reduced Ig levels, absent IgE, and impaired specific antibody responses. The EoE was not diet-responsive, and the authors discussed that there may be endotypes of eosinophilic esophagitis that are clearly independent of immunoglobulin-related mechanisms. Regarding treatment of EoE, swallowed viscous budesonide has been one effective modality often using sucralose as a vehicle; a study by Lee et al¹⁶⁶ showed that viscous budesonide can likely be used effectively with a variety of other vehicles, such as apple sauce, honey, pear sauce, and rice cereal.

Hypereosinophilia and hypereosinophilic syndromes (HES) have a variety of manifestations.^{167,168} Williams et al¹⁶⁸ noted that there are a paucity of data on these disorders in children and sought to characterize the causes of hypereosinophilia in children and to contrast pediatric and adult patients with HES. They evaluated 254 adults and 37 children with unexplained eosinophilia. They found similar frequencies of HES variants between children and adults, but noted that primary immunodeficiency was a more common secondary cause of HES in children (5% vs 0.4% in adults). Excluding subjects with treatable secondary causes, the median peak absolute eosinophil count was increased in pediatric subjects (9376 vs 5543/ μ L; $P = .002$). The children had more gastrointestinal complaints (62% vs 34%; $P = .003$) and less pulmonary involvement (34% vs 59%; $P = .01$) than adults. The authors noted that corticosteroid responsiveness and overall prognosis were similar between the adults and children, and the authors suggested that diagnostic and treatment algorithms used in adults should be applicable to children.

IMMUNODEFICIENCY

Many important and novel studies on immunodeficiency were published in 2016 in *JACI: In Practice*. As noted above, primary immunodeficiency (dedicator of cytokinesis 8 deficiency and X-linked lymphoproliferative disease) was found significantly more frequently in children (5%) compared with in adults (0.4%) with unexplained eosinophilia $\geq 1.5 \times 10^9$ /L on at least 2 occasions at least 1 month apart in a cohort of 291 subjects (13% children and 87% adults).¹⁶⁸ Exome sequencing demonstrated methylenetetrahydrofolate dehydrogenase deficiency as a cause of combined immunodeficiency and megaloblastic anemia in 2 affected siblings with a deletion involving exon 13.¹⁶⁹ Folinic acid treatment led to immune reconstitution in both siblings, enabling discontinuation of all prophylactic therapies.

This precision curative treatment with life-long folinic acid was made possible by specific molecular diagnostics.¹⁶⁹

A case report of a 20-year-old woman with combined immunodeficiency caused by dedicator of cytokinesis 8 (DOCK8) deficiency and impaired organ function reported that related donor hematopoietic stem cell transplantation and post-transplantation cyclophosphamide were effective treatments.¹⁷⁰ IgG4-related bronchial disease due to IgG4 plasma cell infiltration into systemic organs is traditionally treated with systemic corticosteroids. In a 50-year-old man with only pulmonary involvement of IgG4-related disease, fluticasone propionate, at a dosage of 400 mcg/day for 3 months, was successful in reducing pulmonary IgG4-positive plasma cells and thickening in the airway walls and improving clinical outcomes.¹⁷¹ Enteral immunoglobulin was effective in eradicating persistent symptomatic norovirus in the nuclear factor-kappa B essential modulator (NEMO) syndrome (ectodermal dysplasia and immunodeficiency).¹⁷² A comprehensive review updated the epidemiology of and new therapies for enteroviral infections in X-linked agammaglobulinemia.¹⁷³ Whole-exome sequencing in a 13-month-old child manifesting multisystem hyperinflammatory disease without mycobacterial disease identified homozygous loss-of-function signal transducer and activator of transcription 1 (STAT-1) mutation as the cause.¹⁷⁴ Stem cell transplantation was successful in this child. A review of the 4 phenotypes resulting from the 27 reported STAT-1 mutations was also included in this report.¹⁷⁴

Nucleotide-binding oligomerization domain containing 2 (NOD2), a cytoplasmic molecule, helps sense microbial wall components and regulates inflammation and apoptosis. Variants in NOD2 may be associated with inflammatory diseases (NAID) and Crohn's disease. Evidence of immune deficiency was presented in 7 patients with NAID.¹⁷⁵ The immune phenotype of the CHARGE syndrome (Coloboma, Heart disease, choanal Atresia, growth/mental Retardation, Genitourinary malformations, Ear abnormalities) was reported.¹⁷⁶ Despite recurrent ear and pulmonary infections, only 2 of 21 patients with the CHARGE syndrome showed evidence for an immune defect (reduced serum IgA level), suggesting that immunodeficiency is not a component of the syndrome, despite lymphopenia.

Three articles published in *JACI: In Practice* in 2016 were on the topic of common variable immune deficiency (CVID). A proposed new definition of CVID that excluded patients with T-cell defects was reported to improve the accuracy of CVID diagnosis.¹⁷⁷ To help to assess the impact of CVID on patients, a questionnaire, named the CVID-QoL questionnaire, was developed and validated.¹⁷⁸ The questionnaire properties evidenced reliability and construct validity and should help to monitor the quality of life of patients with CVID. Finally, the International Consensus Document (ICON): Common Variable Immunodeficiency Disorders based on critical literature review was presented in its entirety.¹⁷⁹ The document presented the consensus definition of CVID, its epidemiology, natural history, clinical manifestations, associated complications, genetics, diagnosis, and management, and areas for further study. This comprehensive document should be an indispensable resource to all allergists/immunologists and other clinicians treating CVID.

We dedicated a Theme Issue to immunodeficiency disorders with insightful reviews to refresh and update our clinician readers. The array of clinical phenotypes associated with the congenital defects of the hyper-IgM syndromes was highlighted

with emphasis on clinical manifestations, relevant immunologic testing, inheritance patterns, molecular diagnosis, presumed pathogenesis, and immunologic diagnosis and management.¹⁸⁰ Given the high frequency and major morbidities/mortality associated with chronic lung disease in primary antibody deficiencies, a review focused on its recognition, diagnosis, and treatment, particularly distinguishing the features of bronchiectasis and interstitial lung disease.¹⁸¹ The review emphasized that immune dysfunction characterizes interstitial lung disease necessitating immunomodulatory approaches in addition to immunoglobulin replacement and prophylaxis antibiotics. Because immunocompromised patients evidence susceptibility to vaccine-preventable infections, a review addressed this critical vaccination issue.¹⁸² The review presented clear recommendations based on available evidence for use of both routine and specialized vaccines based on the specific immune compromise of the immunodeficiency disorders. The nuts and bolts of immunoglobulin replacement for antibody deficiency, including selection of the optimal choice of product, mode of administration, and site of care, were presented in another review.¹⁸³

In another theme review, the comprehensive multidisciplinary approach needed to successfully diagnose and manage children and adults with chronic granulomatous disease was described and reported to require a 3-prong prophylactic approach, including antibacterial and antifungal agents and interferon-gamma therapy.¹⁸⁴ A novel approach to enhance adherence was also presented. Given the broad spectrum of autoimmune comorbidities seen in primary immunodeficiency disease (PID), a theme review focused on the strategies needed for the successful treatment of autoimmune cytopenias, rheumatologic disorders, and gastrointestinal diseases coexisting with PID.¹⁸⁵

Although PID usually presents during childhood, recently PID has been reported in adults. Given the differences in both physiology and pathophysiology of PID in adults compared with children, the clinical presentation manifestations, diagnosis, and management of PID in adults were reviewed.¹⁸⁶ Finally, a case of a 22-year-old man with hemoptysis and elevated serum IgE level was critically discussed in the light of the differential diagnosis and treatment of the hyper-IgE syndrome.¹⁸⁷

CONCLUSIONS

The breadth and depth of the articles published in 2016 in *JACI: In Practice* were substantial. We hope this review will help our readers consolidate and use this extensive and practical knowledge for the benefit of their patients. We look forward to the clinically impactful information and advances that will appear in *JACI: In Practice* in the coming years.

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