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

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FEATURE ARTICLES

Digital mRNA Profiling in EoE:A Glimpse into the Future

Symptoms plus tissue eosinophil counts are the gold standard for diagnosis of esophageal eosinophilia (EoE). But in clinical practice, it's difficult to make the distinction between eosinophilia associated with EoE versus reflux esophagitis (RE). Previous reports have described a tissue-specific transcriptome, reflecting the specific inflammatory pathways involved with EoE. This study evaluated a method using digital mRNA profiling of esophageal biopsies to differentiate EoE from RE and normal tissue.

The researchers used the nCounter system to measure mRNA expression for 79 target genes, based on previous microarray data. A three-class diagnostic model was created using a training set of proximal and distal esophageal samples from 35 children with a clinicopathologic diagnosis of EoE, 30 with RE, and 30 with normal tissue histology. The model was validated in a blinded predictive set including 18 patients with EoE, 13 with RE, and 16 with normal histology.

A model based on ten genes correctly distinguished children with EoE from those with RE or normal histology, with 100% sensitivity and specificity. In the predictive set, sensitivity in correctly predicting EoE was 78% in distal esophageal biopsies and 89% in proximal specimens. There were no false-positive findings of EoE in the RE or normal groups. When the best predictive distal or proximal biopsy was used, sensitivity increased to 94%.

Initial study shows promising results with digital mRNA profiling for diagnosis of EoE. The study method has high diagnostic sensitivity and specificity, with no false-positive results. If this approach is successful in diagnosing EoE at the first biopsy, it could allow faster initiation of specific treatment. • • •

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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 Asthama
- 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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COMMENT: Diagnosing EoE is not always straightforward. The specificity of tissue eosinophilia is hampered by the fact that RE may cause the same finding. These investigators from Boston evaluated an eosinophil transcriptome utilizing ten genes and found it to be highly sensitive (94%) and quite specific, with no false positives seen in RE patients. This high-throughput digital mRNA expression platform is not yet cost effective—but over time, with improvement in technologies, it may become less expensive and could then be of potential clinical use.

D.A.K.

Lexmond WS, Hu L, Pardo M, et al: Accuracy of digital mRNA profiling of oesophageal biopsies as a novel diagnostic approach to eosinophilic oesophagitis.
Clin Exp Allergy. 2015;45:1317-1327.

ASTHMA RISK CORNER

C-Sections and Asthma Risk: New Data from China

The microbiome of infants delivered by cesarean section differs from those delivered vaginally. Studies from developed Western countries have suggested a possible increase in asthma and wheezing for children with cesarean delivery, although more recent studies from other settings have reported inconsistent results. This study evaluated the relationship between mode of delivery and allergic disease outcomes for children in Hong Kong.

The prospective birth cohort study included 8,327 Chinese children born in Hong Kong: a developed but non-Western country with a high cesarean section rate. Mode of delivery was evaluated for association with childhood hospitalizations for asthma, bronchitis, and bronchiolitis from age 9 days to 12 years. Analyses accounted for potential confounders such as sex, birth and prenatal characteristics, and socioeconomic position.

Mode of delivery was cesarean for 27% of the children. Through age 12, there was no association between mode of delivery and childhood hospitalizations for asthma and wheezing disorders. Risk estimates were higher, but still nonsignifcant, for children living in public rental housing at birth (who are most likely to use public hospitals). There was also no significant association on follow-up to age 2, although residual confounding by socioeconomic position could not be ruled out.

This study from Hong Kong shows no significant difference in allergic disease hospitalizations for children with cesarean vs vaginal delivery. Rates of childhood wheezing outcomes may differ by setting, rather than being biologically mediated. More research is needed to see how the microbiome and mode of delivery affect childhood asthma and other wheezing disorders.

COMMENT: Several studies have suggested that the mode of delivery may affect the development of asthma (Bager P, et al: Clin Exp Allergy. 2008;38:634-642; Thavagnanam S, et al: Clin Exp Allergy 2008; 38:629-633). Leung et al further this research by exploring the association of mode of delivery with hospitalizations for asthma and other wheezing disorders in a developed, non-Western setting • • •

with high rates of Caesarean section. They do so by performing a prospective birth cohort of over 8,000 Chinese children in Hong Kong, and found that they were unable to demonstrate an association.

J.J.O.

Leung JYY, Li AM, Leung GM, Schooling CM: Mode of delivery and childhood hospitalizations for asthma and other wheezing disorders. Clin Exp Allergy. 2015;45:1109-1117.

Post-Bronchodilator FEV_1 Predicts Exacerbation Risk

Several measures, beyond asthma control, have been suggested for use as predictors of exacerbation risk. Some clinical tool for identifying patients at risk of severe asthma exacerbations or poor treatment response might help to guide treatment selection. Using data from asthma treatment trials, the authors developed and evaluated a simple risk score for exacerbations (RSE).

Data were drawn from three studies comparing budesonide/formoterol maintenance and reliever therapy (3,172 patients) with fixed-dose inhaled corticosteroid/long-acting β_2-agonist therapy (4,274 patients) for asthma. Enrolled patients had asthma symptoms not controlled on Global Initiative for Asthma (GINA) treatment steps 3 and 4 and one or more exacerbations.

Baseline data were analyzed to identify the most important predictors of uncontrolled asthma at 3 months and for severe asthma exacerbations within 12 months after the start of treatment. An RSE was developed using data from two-thirds of the patients, and validated in the remaining one-third.

Multivariate analysis identified four "dominant" predictors for uncontrolled asthma and severe exacerbations: GINA step, reliever medication use, postbronchodilator FEV_1, and the five-item Asthma Control Questionnaire score. Smoking and asthma symptom scores were additional dominant predictors for uncontrolled asthma, while body mass index was an additional predictor for severe exacerbation.

The RSE using the five predictors for exacerbations identified patients ranging from low to high 6-month exacerbation risk of 5% to 40%. With adjustment for the selected predictors, budesonide/formoterol reduced exacerbation risk by nearly one-third, compared to fixed-dose inhaled corticosteroid with long-acting β_2-agonist.

While prospective validation is needed, the RSE developed in this study can predict the 3-month risk of uncontrolled asthma and 12-month risk of severe exacerbations. Based on simple clinical assessments, the RSE may provide useful information to guide asthma management.

COMMENT: Using data from three large asthma treatment studies, these authors analyzed 16 patient characteristics to develop an RSE. The fact that post-bronchodilator FEV_1 is included in the RSE is of interest, since it tends to predict persistent airflow limitation—in contrast to prebronchodilator FEV_1, which is considered a marker of control. Other characteristics contributing to the RSE included high body mass index, use of relievers, Asthma Control Questionnaire score and GINA treatment step. The authors suggest that this tool could enable a more "personalized" approach to asthma management.

S.M.F.

Bateman ED, Buhl R, O'Byrne PM, et al: Development and validation of a novel risk score for asthma exacerbations: the risk score for exacerbations. J Allergy Clin Immunol. 2015;135:147-164.

Models Predict Exacerbation Risk in Children

Exacerbations are a major source of morbidity and costs in pediatric asthma. The factors associated with exacerbation risk in children with asthma—particularly seasonal exacerbations—remain unclear. This study sought to identify specific characteristics associated with seasonal exacerbations of asthma among inner-city children.

The retrospective analysis included data on 400 children and adolescents, aged 6 to 20 years, who were controls in two recent Inner-City Asthma Consortium studies. The children's median age was 13 years; 54.5% were male and 59.0% African American. A wide range of demographic and historical variables—including spirometric findings, asthma control, and treatment requirements—were evaluated as risk factors for seasonal exacerbations.

During follow-up, 37.5% of participants had exacerbations. Exacerbations occurred during fall in 28.8% of children, spring in 19.9%, winter in 15.9%, and summer in 14.5%. On univariate analysis, reduced pulmonary function was a risk factor for exacerbations during any season. Exacerbations during the previous season were significant for all seasons except spring.

On multivariate analysis, the strongest predictor of exacerbation during the fall and winter was exacerbation during the previous season. For spring and summer, higher inhaled corticosteroid dose requirement was the strongest factor. Multivariate models had the highest predictive value for fall exacerbations, explaining 30.5% of the variance. Models incorporating the same seven risk factors identified high- and low-risk participants during all four seasons.

For inner-city children with asthma, different risk factors affect the risk of exacerbations at different times of year. The findings may aid in developing effective preventive strategies for reducing seasonal exacerbations. Further studies of exacerbation risk factors are needed, particularly for the winter and spring.

COMMENT: Understanding the factors that increase the risks for exacerbation of asthma in children can help to improve control. These authors used data from two large studies of inner-city children with asthma and ana-

lyzed a variety of predictors for seasonal asthma exacerbations, including flare during the prior season, positive skin tests, elevated total IgE, increased exhaled nitric oxide, pulmonary function test reductions, and atopy to dust mites and cockroach. Multivariate models determined that these predictors had the best predictive power for fall season exacerbations. Limitations included the population studied and relatively limited duration. However, the conclusions suggest that knowing the important predictive factors could help manage asthmatic children at risk for exacerbation during various seasons.

S.M.F.

Teach SJ, Gergen PJ, Szefler SJ, et al: Seasons risk factors for asthma exacerbations among inner-city children.

J Allergy Clin Immunol. 2015;135:1465-1473.

What Factors Affect LOS for Pediatric Asthma?

More than 265,000 pediatric asthma hospitalizations occur each year, with estimated costs of nearly $1 billion. Little is known about the factors affecting length of stay (LOS) in these hospitalizations. This study examined risk factors for prolonged LOS in children hospitalized for asthma.

Using the Pediatric Health Information System, the researchers identified 25,900 children and adolescents (aged 2 to 17) hospitalized for asthma in 2011. Sociodemographic, temporal, health-related, and hospital characteristics associated with LOS were analyzed, with adjustment for severity of illness.

The mean LOS for pediatric asthma hospitalizations was 1.9 days. Several demographic, clinical, regional, and temporal factors associated with greater LOS were apparent. On multivariable analysis, significant risk factors for LOS of more than 2 days were obstructive sleep apnea, odds ratio (OR) 2.3; age 13 to 17, OR 1.3; obesity, OR 1.3; complex chronic health conditions, OR 1.3; winter admission, OR 1.2; female sex, OR 1.1; and weekend admissions, OR 1.1. Prolonged LOS was less likely for summer admissions.

The findings identify a diverse set of factors associated with an increased risk of prolonged LOS in pediatric asthma hospitalizations. Interventions targeting high-risk children—perhaps especially those with sleep apnea, obesity, and complex chronic conditions—might help to prevent prolonged hospital stays.

COMMENT: Asthma is the most common cause of pediatric hospitalization, but little is known about the causes of prolonged LOS. In this study, children with longer hospital stays tended to be older and female, more often had obstructive sleep apnea, and were more likely to be admitted on a weekend or in winter. Targeting interventions to address these risk factors may affect length of stay for pediatric asthma.

C.C.R.

Shanley LA, Lin H, Flores G, et al: Factors associated with length of stay for pediatric asthma hospitalizations.

J Asthma. 2015;52:471-477.

Before and After ICU Admission, Children Don't Receive Recommended Asthma Care

The number of children hospitalized for asthma who are admitted to ICUs appears to have increased in recent decades. Most studies of these hospitalizations have focused on short-term management and outcomes; little is known about the long-term care received by these children, before and after hospitalization. This study examined the characteristics of children with asthma admitted to the ICU, including their rates of guideline-recommended outpatient care before and after hospitalization.

The analysis included 385 children and adolescents (aged 2 to 17) hospitalized for asthma at 14 participating centers during 2012-13. Of these, 34% were admitted to the ICU. Factors associated with ICU admission were evaluated, along with two preventive factors: inhaled corticosteroid use and evaluation by an asthma specialist in the period before and after hospitalization.

Three factors were independently associated with ICU admission: female sex, odds ratio (OR) 1.97; public insurance status, OR 1.88; and current inhaled corticosteroid use as an indicator of more severe chronic asthma, OR 2.10. Evaluation by an asthma specialist was a significant protective factor: OR 0.46.

As a group, the children admitted to the ICU had low rates of guideline-recommended outpatient care. Only 65% were taking ICSs at the time of admission, while just 19% had previous specialist evaluation. At discharge, ICSs were prescribed to 85% of ICU-treated children who had not previously used controller medications. Sixty-two percent were referred to an asthma specialist within 3 months after hospitalization with ICU admission.

About one-third of children hospitalized for asthma receive ICU care. Before and after their hospital stay, these children receive suboptimal asthma care. The authors emphasize the need for prevention-oriented asthma management in all clinical encounters.

COMMENT: Pediatric asthma ICU admissions have increased up to sixfold since the 1990s, and account for one-third of asthma admissions in children. In this large, multicenter, observational study, risk factors for ICU admission included female sex, public insurance, and two guideline-related factors: chronic asthma severity and lack of asthma specialist consultation. This study teaches us of the importance of educating our primary care colleagues in the guideline-recommended co-management of severe pediatric asthma.

C.C.R.

Hasegawa K, Ahn J, Brown MA, et al: Underuse of guideline-recommended long-term asthma management in children hospitalized to the intensive care unit: a multicenter observational study.

Ann Allergy Asthma Immunol. 2015;115:10-16.

Collaborating with Pharmacists to Improve Asthma Care

Community pharmacies provide an opportunity for collaborations to increase use of effective asthma therapies, potentially improving outcomes for high-risk patients. The authors developed a measure of asthma medication fills, and assessed its relationship to asthma-related utilization in one metropolitan area.

Data from 27 community pharmacies in the Cincinnati area were used to calculate a pharmacy-level Asthma Medication Ratio (AMR), calculated as asthma controller medication fills divided by controller plus rescue fills. A higher AMR value reflected more filled controller prescriptions, compared to rescue prescriptions.

The AMR was compared with asthma-related utilization in the same census tract, calculated by dividing all emergency visits and hospitalizations by the number of children in the tract. The analysis accounted for ecological measures of poverty and access to care.

The study included pharmacy data on about 35,500 filled prescriptions between 2010 and 2012. Median AMR was 22.4 visits per 1,000 child-years, with wide variation across census tracts: from 1.3 to 60.9 per 1,000 child-years. For tracts with an AMR of less than 0.5, asthma-related utilization was substantially higher: 26.1, compared to 9.9 for tracts with an AMR of 0.5 or higher. After adjustment for poverty and access, each 0.1 increase in AMR was associated with a 9.5 decrease in utilization rate. Although fills varied seasonally, pharmacies in high-utilization tracts filled more rescue than controller prescriptions at almost all times.

A pharmacy measure of asthma medication fills is independently related to asthma-related utilization by children. Collaborating with pharmacies could provide a useful new approach to assessing and improving childhood asthma care and control at the community level.

COMMENT: This novel analysis links the asthma medication ratio—the ratio of asthma controller prescriptions filled to all asthma prescriptions filled—assessed at individual community pharmacies with pediatric asthma exacerbations within the geographical census tract of the pharmacy. The results showed a decrease of nearly 10 asthma exacerbations per 1,000 children per year for each 0.1 increase in the pharmacy-level AMR. This innovative study demonstrates that collaborative relationships between physicians, community pharmacists, and patients (and families) may generate development of quantifiable interventions aimed at reducing asthma morbidity. Also see the related editorial by Vernacchio: Pediatrics. 2015; 135:1133-1134.

C.D.

Beck AF, Bradley CL, Huang B, et al: The pharmacy-level asthma medication ratio and population health.
Pediatrics. 2015;135:1009-1017.

Distress and Asthma Control: How Do They Affect Productivity?

Patients with asthma are at increased risk of psychologic distress (PD), which leads to increased healthcare resource use and reduced work productivity. Little is known about how asthma control and PD may interact to affect the burden of asthma. This study looked at the combined effects of these two factors on productivity loss in working adults with asthma.

As part of a larger prospective study of the costs and life impact of asthma, the analysis included 300 employed Canadian adults with asthma. Validated measures were used to assess PD and productivity loss due to absenteeism and presenteeism. Asthma control was assessed based on Global Initiative for Asthma criteria. In addition to the contributions of PD and uncontrolled asthma to productivity loss, the study analyzed the effects of PD subtypes, based on the presence of depression and/or anxiety symptoms.

Asthma was controlled in 20% of patients, partially controlled in 40%, and uncontrolled in 40%. Rates of PD were 34% overall, 24% in patients with controlled asthma, 32% in those with partially controlled asthma, and 42% in those with uncontrolled asthma.

Compared to patients with controlled asthma and without PD, weekly productivity loss (in Canadian dollars) was $286 for those with uncontrolled asthma and no PD and $465 for those with uncontrolled asthma plus PD. There was no significant interaction between PD and asthma control in terms of productivity loss. Depression affected productivity loss only in patients with controlled asthma, whereas anxiety was associated with productivity loss at all levels of asthma control.

Uncontrolled asthma is linked to increased productivity loss only in patients without PD. That finding reflects the high productivity impact on PD, with minimal additive impact of uncontrolled asthma. The authors call for further studies to evaluate the cost-effectiveness of interventions targeting PD in patients with asthma.

COMMENT: The psychologic distress that may coexist with asthma has a significant societal and personal impact. Uncontrolled asthma is associated with high productivity loss. The contribution of PD is so large (38% increase) that the synergistic effects of poorly controlled asthma cannot be discerned. This is an important observation that points to the need to clearly investigate the psychologic health of our patients with chronic respiratory disease.

B.E.C.

Moulle GJ, FitzGerald JM, Rousseau R, et al: Interaction effect of psychological distress and asthma control on productivity loss?
Eur Respir J. 2015;45:1557-1565.

When Seeing an Asthma Specialist, No Added Benefit of Written Action Plan

Guidelines recommend a written asthma action plan to help patients recognize and respond to changes in asthma status. But the strength of the evidence behind this recommendation has been questioned. This trial evaluated the efficacy of the written asthma action plan, provided by subspecialists as part of usual care for asthma.

The study included 407 adult and pediatric patients with persistent asthma, making their initial visit to pulmonary and allergy practices at four New York City hospitals. One group received a written asthma action plan, with a standard form completed by the physician. Controls received no written instructions, other than prescriptions. Various efficacy outcomes were compared between groups.

None of three primary outcomes—asthma symptom frequency, emergency visits, or asthma-related quality of life from baseline to 1-year follow-up—was significantly improved for patients receiving a written asthma action plan. The two groups had similar and significant reductions in daytime and nighttime asthma symptoms, β-agonist use, and emergency visits. Both groups also showed improvements in quality of life for adult patients and for caregivers of pediatric patients.

The study finds no evidence that a written asthma action plan improves outcomes for patients with persistent asthma. However, it does show significant benefits for patients receiving medical care and education from an allergist or pulmonologist. Further studies are needed to evaluate the benefits of the written asthma action plan for patients treated in primary care.

COMMENT: This long-term study supports the value of specialty evaluation and care for asthma. It is surprising that a written asthma management plan did not bring significant benefit. However, it is comforting to know that the major benefit occurs when the specialist physician establishes a relationship with the patient that includes education, asthma management, and follow-up.

B.E.C.

Sheares BJ, Mellins RB, Dimango E, et al: Do Patients of Subspecialist Physicians Benefit from Written Asthma Action Plans?
Am J Respir Crit Care Med. 2015;191:1374-1383.

For Some Obese Patients, Autoinjector Needles Are Too Short

Early use of self-administered adrenaline autoinjectors can be lifesaving in patients with anaphylaxis. However, amid the ongoing obesity epidemic, there is concern that autoinjector needles may be too short to reliably deliver intramuscular (IM) adrenaline in many patients. This issue was examined in a population of adult allergy patients.

The study included 28 patients with a history of anaphylaxis who had been prescribed an adrenaline autoinjector. There were 23 women and 5 men, with body mass index (BMI) ranging from 18 to 44. Ultrasound was used to measure the skin-to-muscle depth (STMD) in the anterolateral and anterior thigh.

In 68% of patients, the anterolateral thigh STMD was greater than the autoinjector needle length of 15.02 mm. In the anterior thigh, this proportion decreased to 50%. The anterolateral thigh depth exceeded the needle length for 87% of women, compared to none of the men. Only 1 of 16 patients with a BMI greater than 30 had an anterolateral thigh STMD smaller than the needle length.

For many adult allergy patients, the subcutaneous tissue may be too thick for reliable IM drug delivery using an adrenaline autoinjector. This risk is greater for women, including many in the normal BMI range, as well as in obese patients.

COMMENT: Recent guidelines have reinforced that autoinjectible epinephrine is first-line treatment of anaphylaxis in the field. Injection in the region of the vastus lateralis muscle is recommended, as studies in normal subjects have demonstrated that peak plasma epinephrine levels occur in 8 minutes with IM injection, compared to 34 minutes with subcutaneous injection. With the rise of obesity, there are concerns about the potential for suboptimal epinephrine deposition. Building on previous reports, this study prospectively examined the STMD in vastus lateralis region of 28 patients with history of anaphylaxis. Based on ultrasound measurements, the autoinjector needle length was suboptimal for 68% of this population. Risk factors for suboptimal needle length included female gender and a BMI greater than 30. The authors recommend that epinephrine autoinjectors be developed with longer needles to ensure IM administration.

J.J.O.

Johnstone J, Hobbins S, Parekh D, O'Hickey S: Excess subcutaneous tissue may preclude intramuscular delivery when using adrenaline autoinjectors in patients with anaphylaxis. Allergy. 2015;70:703-706.

COPD RISK CORNER

Blood Eosinophils: Worth Checking in COPD Too!

Some simple biomarker is needed to identify patients with chronic obstructive pulmonary disease (COPD) who will benefit from inhaled corticosteroids (ICS). Several studies have found improved short-term responses in patients with airway eosinophilia. Blood eosinophil count was evaluated as a predictor of long-term outcomes of ICS therapy in COPD.

The researchers analyzed data from two randomized, 12-month trials of ICS for patients with moderate-to- • • •

severe COPD and a history of exacerbations. All patients received vilanterol 25 μg once daily, with or without the addition of fluticasone furoate, 50, 100, or 200 μg. Exacerbation rates were compared for patients at different levels of baseline blood eosinophil count. Lung function measures and pneumonia incidence were compared as well.

Of the 3,177 patients included in the study, 66% had a baseline eosinophil count of 2% or higher. For all patients with a blood eosinophil level of at least 2%, adding fluticasone at any dose was associated with a 29% reduction in exacerbations: mean 0.91 vs 1.28 exacerbations per patient per year. For those with eosinophil counts of less than 2%, the reduction was only 10%: 0.79 vs 0.89.

Even larger reductions in exacerbations were achieved with fluticasone in patients with higher eosinophil counts. With vilanterol alone, exacerbation rate increased at each level of eosinophil count. The improvement in trough FEV_1 and the increase in pneumonia risk with fluticasone were unrelated to eosinophil level.

Blood eosinophil count may be a useful and simple biomarker of 1-year response to inhaled corticosteroid in patients with COPD. Further study is needed to confirm this approach to choosing the best strategy for reducing exacerbation risk.

COMMENT: Maybe at least some patients with COPD behave like asthmatics. This study certainly reinforces that potential. The authors found that in a group of moderate-to-severe COPD patients, when comparing use of long-acting beta agonist (LABA) as monotherapy compared to combination LABA and ICS, reduction in exacerbations was correlated to the baseline eosinophil count. Compared to LABA alone, the addition of ICS reduced exacerbations by 24% with baseline eosinophil counts between 2% and 4%, 32% with counts of 4% to 6%, and 42% with counts of 6% or higher.

J.J.O.

Pascoe S, Loncantore N, Dransfield MT, et al: Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials.
Lancet Respir Med. 2015;3:435-442.

Paradigm Shift in COPD Pathogenesis

Acceleration of the normal age-related decline in FEV_1 has been considered a key characteristic of COPD. But recent studies have reported variable and smaller than expected declines in FEV_1, especially in patients with severe airflow limitation. This study evaluated a possible alternative course in which COPD occurs in patients with low maximally attained lung function in early adulthood.

Subjects enrolled in three independent cohort studies were stratified according to FEV_1 of greater than or less than 80% of predicted at cohort inception, at which time the mean age was about 40 years. After 22 years of observation, the presence or absence of COPD was assessed. The ability of rate of decline in FEV_1 to explain the diagnosis of COPD was assessed for patients with a normal or low initial FEV_1.

The study included 657 participants with an initial FEV_1 of less than 80% predicted and 2,207 with an FEV_1 of at least 80% predicted. During follow-up, COPD developed in 26% of patients with a low FEV_1 versus 8% of those with a normal FEV_1.

Of the total number of participants who developed COPD, about half had a normal FEV_1 before age 40, followed by an average yearly decline of 53 mL. For those with an initial low FEV_1, the average decline was 27 mL per year, with no difference in smoking history.

Some patients who develop COPD have a low FEV_1 in early adulthood, followed by a normal age-related decline. The results suggest that an accelerated decline in FEV_1 is not always part of the course of COPD. Risk of COPD is threefold higher for individuals with a baseline FEV_1 of less than 80% predicted before age 40, compared to those with normal FEV_1.

COMMENT: The prevailing paradigm of COPD pathogenesis has been that, in predisposed individuals, tobacco smoke exposure results in clinical disease through accelerated age-related decline in lung function, as assessed by the FEV_1. This has triggered numerous therapeutic trials aimed at reducing the rapid decline in FEV_1. This fascinating study suggests that a low FEV_1 in early adulthood may result in COPD—without a subsequent rapid decline in FEV_1. These data add significantly to our paradigm of COPD pathogenesis. See also the related editorial by Speizer and Ware: N Engl J Med. 2015; 373:185-186.

C.D.

Lange PE, Celli B, Agustí, et al: Lung-function trajectories leading to chronic obstructive pulmonary disease.
N Engl J Med. 2015; 373:111-122.

Serum Bilirubin: A New Biomarker for COPD?

Oxidative stress plays a key role in COPD progression, suggesting that serum bilirubin might be a useful biomarker. Bilirubin has potent antioxidant actions, and higher bilirubin levels have been shown to protect against oxidative stress. Data from a large cohort study were used to assess the association between serum bilirubin and COPD progression.

The analysis included 4,680 smokers (aged 35 to 60) with mild to moderate airflow limitation, drawn from the Lung Health Study. Serum bilirubin was measured, and its relationships to postbronchodilator FEV_1 and the rate of FEV_1 decline were assessed. Potential associations with overall and disease-specific mortality were analyzed as well.

Serum bilirubin was positively associated with FEV_1,

after adjustment for age, sex, race, BMI, and smoking history. There was also a negative association between bilirubin and annual decline in FEV_1. Higher bilirubin levels were associated with a lower rate of death from coronary heart disease, but unrelated to other mortality outcomes.

Serum bilirubin is associated with lung function and disease progression in patients with mild to moderate COPD, independent of smoking history. Patients with higher bilirubin levels have higher FEV_1, slower decline in FEV_1, and less coronary heart disease mortality. With further study, bilirubin may be a useful and practical COPD biomarker.

COMMENT: Oxidative stress plays a significant role in COPD, and bilirubin has been shown to be an efficient scavenger of free radicals. These authors analyzed the Lung Health Study, looking at the relationship between serum bilirubin and COPD severity and progression. Serum bilirubin was positively correlated with FEV_1 and negatively related to the annual decline in FEV_1 as well as the risk of death from coronary artery disease. While the authors suggest bilirubin may be a useful biomarker for COPD, the marked overlap in values brings into question its clinical utility. Clearly, further prospective studies will be required to validate bilirubin as a useful biomarker.

D.A.K.

Apperley S, Park HY, Holmes DT, et al: Serum bilirubin and disease progression in mild COPD.
Chest. 2015;148:169-175.

Does GERD Cause Rhinitis?

In addition to its impact on quality of life, non-infectious rhinitis (NIR) is a possible risk factor for asthma. The proposed association between gastroesophageal reflux disease (GERD) and chronic rhinosinusitis suggests a relationship with upper airway inflammation. This study sought to clarify the relationship between nocturnal GERD and NIR.

As part of a longitudinal, population-based study, 5,417 Northern European adults (born between 1945 and 1973) were assessed by questionnaires in 1999-2001 and 2010-12. Nocturnal GERD was evaluated as a risk factor for NIR, along with age, sex, BMI, smoking, and asthma. The study definition of NIR was nasal obstruction, secretion, and/or sneezing in the absence of the common cold.

During a decade of follow-up, NIR developed in 19.1% of subjects. The rate of NIR was 2.8% for participants who reported nocturnal GERD on both questionnaires, compared to 1.2% for those without nocturnal GERD. The higher the frequency of reflux episodes on the first questionnaire, the higher the risk of developing NIR. On adjusted analysis, the odds ratio for NIR among subjects reporting nocturnal reflux symptoms at least three times weekly was 1.6. Smokers were at higher risk of both NIR and nocturnal GERD.

Based on this 10-year follow-up study, nocturnal GERD is a significant risk factor for NIR. Smoking, asthma, and female sex are additional risk factors. The possibility of nocturnal GERD should be considered in patients with rhinitis or rhinosinusitis.

COMMENT: This study explored the association between GERD and the development of non-infectious rhinitis: allergic rhinitis, nonallergic rhinitis, and chronic rhinosinusitis with and without polyps. Over 5,400 subjects answered a questionnaire in 1999-2001 and were then followed for the next decade. More than 19% of this group developed NIR, and this risk was significantly higher for those with nocturnal gastroesophageal reflux. Further, the likelihood of developing NIR increased with the frequency of nocturnal reflux episodes. The authors point out that the association between these two conditions does not prove a causal relationship; they call for further prospective studies in which the study population with nocturnal GERD is stratified into treated and untreated groups and then followed. In the meantime, the researchers suggest that our patients with NIR should be evaluated for nocturnal GERD.

J.J.O.

Schiöler L, Ruth M, Jõgi R, et al: Nocturnal GERD—a risk factor for rhinitis/rhinosinusitis: the RHINE study.
Allergy. 2015;70:697-702.

Climate Change and Ragweed: Effects across the Pond

Ragweed is a major cause of sensitization in North America and parts of Europe. Historically, ragweed is uncommon in the United Kingdom. This study presents new data on rising ragweed pollen levels in one UK area.

The researchers analyzed 44 years of pollen count data in Leicester. Ragweed pollen was detected in 7 of those years; before 2014, the maximum daily average concentration was 5. However, in 2014, this figure peaked at 35. Ragweed pollen was detected mainly on four days in early September.

Added to previous data from Europe, the findings are consistent with a possible role of climate change leading to the occurrence of ragweed pollen in Europe. The northward spread of ragweed could be related to the long-lasting autumns needed for the ragweed seeds to mature. If the UK climate changes to allow naturalization of this plant, as predicted, ragweed pollen allergy could become a new health concern in the United Kingdom.

COMMENT: Ragweed is a very important allergen in much of the United States, but has not been a concern in the United Kingdom. This report evaluated ragweed pollen levels in Leicester and found that ragweed pollen counts spiked to modest levels in 2014. The authors indicate that climate change is making the UK climate more suitable for ragweed growth. Windborne spread from neighboring European countries may be an additional source.

D.A.K.

Pashley CH, Satchwell J, Edwards RE: Ragweed pollen: is climate change creating a new aeroallergen problem in the UK?
Clin Exp Allergy. 2015;45:1262-1265.

Web-Based Reporting May Make Oral Immunotherapy Safer

Reactions during the home phase of oral immunotherapy (OIT) are usually mild to moderate, but are relatively common. Accurate data on home reactions are essential for safe and successful OIT, but compliance with paper diaries is very low. This study evaluated a Web-based electronic reporting system for monitoring of home OIT for food allergy.

Patients used the Web-based reporting system to make daily reports of OIT use. If any reaction occurred, a second screen appeared asking for more detailed information. Over a 15-month period, 157 patients receiving at least 4 weeks of milk, peanut, or egg OIT were instructed in using the system. Reporting rates and OIT outcomes were compared to those of 100 previous OIT patients providing email reports.

The successful reporting rate with the Web-based system—based on daily reports sent on at least 24 consecutive days—was 90%, compared to 75% with email. Previous experience with OIT was the only significant risk factor for failure to report. The odds of successful reporting were about three times higher with the Web-based system, compared to email. Reporting was significantly different for patients with only minor reactions; there was no difference in reporting of severe reactions.

A Web-based system can promote more complete and precise reports of home OIT for food allergy. The system evaluated in this study permits simultaneous monitoring of large numbers of patients, and should be useful for multicenter trials of food allergy treatments.

COMMENT: The use of technology and Web-based programs in the treatment of our patients continues to increase. This study demonstrates the utility of a Web-based program for patients to record OIT dose received and information regarding adverse reactions in real time. As the authors note, reports of minor reactions are important in guiding the treatment protocol so that any necessary changes may be made to improve safety of the oral immunotherapy. This gives allergists "food for thought" as we ask for increased participation from patients in order to improve their medical care.

V.H.-T.

Nachshon L, Goldberg MR, Elizur A, et al: A web site-based reporting system for monitoring home treatment during oral immunotherapy for food allergy.
Ann Allergy Asthma Immunol. 2015;114:510-515.

Negative Histamine Controls in Inpatients–Can We Predict Them?

Inpatient skin testing for pencillin allergy often yields indeterminate results due to negative histamine control results, even after exclusion of H_1 antagonists. Although several medications and other factors have been suggested to affect the results of inpatient skin testing, there are limited data on this issue. This study evaluated factors associated with a negative histamine skin test response in inpatients.

A medical center database identified 52 inpatients with negative histamine test responses, despite the absence of antihistamines for 72 hours before testing. Factors potentially associated with negative histamine control results were evaluated by comparison with 125 controls with normal histamine responses.

Patients with negative histamine results were older than normal controls: mean age 68 versus 60 years. On bivariate analysis, cases were more likely to have an ICU stay: controls versus 60 years for controls. Clinical factors associated with negative histamine responses on regression analysis were ICU stay, odds ratio (OR) 3.76; systemic corticosteroids, OR 8.18; and H_2 blockers, OR 4.90. Older age was also a significant factor: OR 1.04 per year.

For inpatients undergoing skin testing for penicillin allergy, ICU status, systemic corticosteroid treatment, and H_2 blocker use are all significant risk factors for a negative histamine response. Older patients are also more likely to have negative histamine controls. These factors warrant "greater consideration and caution" in performing skin tests for possible antibiotic hypersensitivity.

COMMENT: The practicing allergist may be consulted for suspected drug allergy in the inpatient setting. Few studies have investigated skin testing of patients in the ICU setting. This report found that ICU patients were more likely to have negative histamine control. Patients with negative histamine control during skin testing were more likely to be older than control patients. They were also more likely to be treated with systemic corticosteroids, most used short term, as well as H_2 blockers. These results are important for those of us who are called in to consult in the inpatient setting. Prospective studies are needed to better understand the clinical implications of skin testing, as well as the possible need to repeat testing in some of these patients.

V.H.-T.

Geng B, Thakor A, Clayton E, et al: Factors associated with negative histamine control for penicillin allergy skin testing in the inpatient setting.
Ann Allergy Asthma Immunol. 2015;115:33-38.

Venom Anaphylaxis and Clonal Mast Cell Disorders: New Observations

Patients with hymenoptera venom allergy (HVA) who develop anaphylaxis with hypotension are at risk of underlying systemic mastocytosis. A case report illustrating the diagnosis and management of a case of indolent systemic mastocytosis presenting as hymenoptera venom anaphylaxis is presented.

A 47-year-old man lost consciousness 5 minutes after being stung by a yellowjacket, requiring epinephrine

and fluids for resuscitation. He was started on hymenoptera venom immunotherapy, but had systemic reactions during the buildup phase. A severe anaphylactic reaction to his second maintenance dose required three intramuscular epinephrine injections.

The patient was found to have an elevated tryptase level of 29 ng/mL shortly after this reaction; a baseline level of 25 ng/mL was measured 4 weeks later. He had no cutaneous lesions or other physical findings consistent with mastocytosis. The elevated tryptase levels prompted a bone marrow biopsy, which showed dense, multifocal mast cell infiltrates. Omalizumab was started, and the patient was able to resume venom immunotherapy. He continues on lifelong immunotherapy; on being restung, he had no serious systemic reaction.

In discussing their experience, the authors recommend baseline serum tryptase measurement for all patients with hymenoptera anaphylaxis. If tryptase is elevated, bone marrow biopsy is recommended for possible systemic mastocytosis. The mechanisms of hymenoptera anaphylaxis in mastocytosis are discussed, along with the diagnostic and treatment implications.

Patients with the clonal mast cell disorder systemic mastocytosis are at risk of anaphylactic episodes caused by excessive mediator release by mast cells. Because of its "preferential association" with HVA, systemic mastocytosis should be suspected with severe reactions to hymenoptera stings associated with increased serum basal tryptase levels. This study evaluated the presence of clonal mast cell disorders in patients with hymenoptera-induced anaphylaxis but normal serum tryptase.

The study included 22 patients with severe reactions to hymenoptera stings, with hypotension and/or loss of consciousness, and without urticaria pigmentosa or other suggestive skin lesions. All had normal serum basal tryptase levels—less than 11.4 ng/mL. All patients underwent bone marrow evaluation for diagnosis of clonal mast cell disorders; bone mineral density was assessed in those found to have mastocytosis.

In 16 patients, bone marrow evaluation led to the diagnosis of indolent mastocytosis, while 1 patient had a monoclonal mast cell activation syndrome. Serum tryptase levels were higher in patients with mastocytosis, but this group rarely had angioedema/urticaria associated with hypotension.

This study finds mastocytosis in a large proportion of patients with severe reactions to hymenoptera stings and hypotension, despite normal serum tryptase levels. Absence or urticaria or angioedema may be the factor most strongly associated with the presence of mastocytosis in this situation. The authors discuss the implications for early diagnosis of clonal mast cell disorders in patients with severe HVA and normal tryptase levels.

COMMENT: Castells and colleagues begin by describing a patient with HVA who presents with a systemic hypotensive event and elevated tryptase level. They then present an excellent literature review of mast cell disorders, reminding us that serum tryptase levels should be checked in all patients with systemic reactions to hymenoptera.

The paper by Zanotti et al analyzes 22 patients with HVA who presented with hypotension without skin manifestations and with essentially normal tryptase levels. Interestingly, 16 of them had mastocytosis. The authors suggest that patients with HVA presenting with hypotension without skin lesions are at greater risk for CMD. This is a small study, but it raises interesting questions about when patients with HVA should have bone marrow examinations.

S.M.F.

Castells M, Hornick J, Akin C: Anaphylaxis after hymenoptera sting: Is it venom allergy, a clonal disorder, or both?
J Allergy Clin Immunol Pract. 2015;3:350-355.
AND
Zanotti R, Lombardo C, Passalacqua G, et al: Clonal mast cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels.
J Allergy Clin Immunol. 2015;136:135-139.

Hormones in Atopic Disease– How Much of a Role Do They Play?

Previous studies have suggested that female hormones might contribute to the development of allergic rhinitis and asthma after puberty. This longitudinal study assessed the relationships between age at menarche, hormonal contraceptive use, and new-onset allergic rhinitis and asthma in young women.

As part of the International Study of Asthma and Allergies in Childhood, 1,194 German females were followed up from age 9-11 to age 19-24. In adolescence and young adulthood, the women provided data on age at menarche, use of hormonal contraceptives, and age at onset of doctor-diagnosed asthma and allergic rhinitis.

Overall, 11% of participants had new-onset allergic rhinitis after menarche, while 3% were diagnosed with asthma. Those with late menarche, after age 13, were less likely to develop allergic rhinitis: adjusted odds ratio 0.32. Age at menarche was not significantly related to asthma. However, hormonal contraceptive use was associated with a decreased risk of both outcomes: odds ratio 0.14 for allergic rhinitis and 0.27 for asthma.

Late onset of menarche is associated with a lower risk of developing allergic rhinitis after puberty in girls. Hormonal contraceptive use is inversely related with both new-onset allergic rhinitis and asthma, and thus may have a significant protective effect against respiratory allergies in young women.

COMMENT: This thought-provoking study investigated the presence of atopic disease in girls before and after menarche. Overall, almost three-fourths were treated with a con-

traceptive for at least 1 year by the end of the study. New-onset allergic rhinitis was less likely in patients with either late menarche (after 13 years) or treatment with hormonal contraceptives. Patients using hormonal contraceptives were also less likely to develop new-onset asthma. The authors suggest that exogenous hormones may protect young women from developing allergic rhinitis or asthma after puberty. This is of particular interest since the incidence of the atopic diseases was lower in these patients.

V.H.-T.

Wei J, Gerlich J, Genuneit J, et al: Hormonal factors and incident asthma and allergic rhinitis during puberty in girls.

Ann Allergy Asthma Immunol. 2015;115:21-27.

Grass Pollen: Potency Depends on More than Number of Grains!

Several different factors can affect allergens released from pollen. This study assessed natural variation in release of Ph1 p 5, the major group 5 allergen from grass pollen in Europe.

The study used data on airborne pollen and allergens collected simultaneously at ten European sites for 3 consecutive years. A Ph1 p 5-specific assay was used to measure group 5 allergens in particulate matter larger than 10 μm as well as particulates larger than 2.5 and smaller than 10 μm. Mediator release was assessed in FcεRI-humanized basophils, and daily observed potency was mapped to the origin of the pollen.

Average release of Ph1 p 5 was 2.3 pg per pollen. However, there was wide variation in potency, from less than 1 to 9 pg of Ph1 p 5 per pollen. While the main variation occurred locally day to day, the average potency maps in different parts of Europe varied from year to year.

Mediator release from basophils was more strongly correlated with allergen levels than with pollen grains per cubic meter. The amount of allergen released by pollen varied significantly, depending on humidity level.

The results show significant variation in Ph1 p 5 allergen release by grass pollen, added to variations in pollen count. Levels of allergen in ambient air might provide important information, in addition to pollen counts. During times of high humidity, there may be more allergen on smaller particles, which can reach deeper into the airways.

COMMENT: Timothy grass is the major outdoor allergen in Europe, and although a variety of different antigens have been described, Phl p 5 is considered the most important allergen. Phl p 5 was used as the reference standard for this well-designed study collecting data from ten different sites over 3 years. The most interesting findings are that the allergenic potency of the pollen varied by year and location, even more than previously reported for trees. The researchers also found that increasing humidity may double the allergenic potency. The take-home message for allergists is that it's not just the number of pollen grains that is important—allergenic potency could have an even greater impact for our patients.

S.M.F.

Buters J, Prank M, Sofiev M, et al: Variation of the group 5 grass pollen allergen content of airborne pollen in relation to geographic location and time in season.

J Allergy Clin Immunol. 2015;136:87-95.

Children with Increased IgE–What Happens Over Time?

There are few longitudinal studies of IgE levels in children. The authors present five-year follow-up data in a group of children with high total IgE, including associations with risk factors, allergic diseases, and specific IgE levels.

Seventy-seven children with serum total IgE greater than 100 IU/mL in 2003 (median age 7 years) were reassessed in 2008. In addition to parental interviews and clinical examination, total IgE and specific IgE levels to selected allergens were assessed.

Over 5 years, total IgE levels decreased, in both sexes and in children living in urban and rural areas. Most children were monosymptomatic at baseline, and this group initially had the highest total IgE levels. The percentage of polysymptomatic children increased during follow-up; this group had higher mean total IgE. In 2008, 11.7% of children were still asymptomatic and 11.7% reported relief from allergy symptoms. Most children with normal total IgE levels continued to have allergy symptoms.

On specific IgE measurement, two-allergen sensitization was the most common finding. Mean total IgE levels remained unchanged only for children sensitized to four allergens; those with the highest total IgE levels became sensitized to at least one new allergen. Specific IgE to food allergens decreased over time. However, specific IgE to inhalant allergens increased, even though total IgE decreased.

In children with high serum total IgE, levels decrease over time. Increased or unchanged total IgE may precede the development of polysymptomatic allergy. The results suggest that serial total IgE measurement may help to predict the onset of allergic disease.

COMMENT: Pediatric patients often present with low levels of IgE in early childhood, increasing to peak in the early teen years. In this study, total IgE decreased over 5 years; however, almost 90% of patients continued to have levels above 100 IU/mL. Patients from rural areas had higher levels of total IgE at the beginning of the study, but allergy rates were similar between rural and urban areas. More than one-fifth did not have sensitization to any allergens tested, whether or not total IgE was elevated. The possibility of allergy to other allergens exists. It is interesting to note that patients with allergy to a single allergen had higher total IgE levels. Increasing or stable total IgE levels in patients with allergy may help predict polysymptomatic allergy, as well persistent allergy or

new-onset allergy. Measurements of total IgE over time may help to predict whether atopy will develop.

V.H.-T.

Daniluk U, Alifier M, Kaczmarski M, et al: Longitudinal observation of children with enhanced total serum IgE.

Ann Allergy Asthma Immunol. 2015;114:404-410.

Asthma and Smoking Interact to Increase Risk of Adult Airway Obstruction

Asthma is a major risk factor for adult airway obstruction and chronic obstructive pulmonary disease. Atopy may play a role as well. This study assessed the interaction between smoking and asthma in increasing the risk of airway obstruction, including the contributions of atopy and age at asthma onset.

The study included data on 15,668 European Community Respiratory Health Survey participants who underwent spirometry in 1991-93. Of these, 8,916 underwent repeat spirometry at 9 years' follow-up. Rates of airway obstruction and decreased lung function decline were assessed, including the effects of smoking and early versus late-onset asthma (before versus after age 10).

Early-onset asthma was associated with a sharply increased risk of adult airway obstruction. This was so for both never-smokers, odds ratio (OR) 21.0; and current smokers, OR 23.7. For late-onset asthma, this association differed significantly by smoking status: OR 11.2 for never-smokers versus 25.6 for current smokers. The increase in adult airway obstruction and smoking was stronger for subjects without atopy.

Both early- and late-onset asthma are associated with a 20-fold increase in the risk of adult airway obstruction. However, for the late-onset group, smoking substantially increased the risk of later airway obstruction. The authors discuss possible mechanisms of these associations and their implications for smoking prevention efforts.

COMMENT: The interaction between late-onset asthma and of adult airway obstruction is twice as high in smokers compared to never-smokers, and more significant in nonatopic patients. In patients with asthma, it's extremely important to prevent uptake of smoking in order to prevent reduced lung function and chronic airflow limitation. The increased recognition of asthma-COPD overlap syndrome clearly helps to underline the detrimental effects of smoking, especially in late-onset asthma. See the accompanying editorial by Malcolm Sears (Eur Respir J. 2015;45:586-588).

B.E.C.

Aanerud M, Carsin A-E, Sunyer J, et al: Interaction between asthma and smoking increases the risk of adult airway obstruction.

Eur Respir J. 2015;45:635-643.

REVIEWS OF NOTE

COMMENT: This three-part series by a European Respiratory Society task force is an excellent summary of the evaluation and management of childhood asthma.

B.E.C.

Brand PL, Mäkelä MJ, Szefler SJ, et al: Monitoring asthma in childhood: symptoms, exacerbations and quality of life

Eur Respir Rev. 2015; 24:187-193.

Rottier BL, Eber E, Hedlin G, et al: Monitoring asthma in childhood: management-related issues.

Eur Respir Rev. 2015;24:194-203.

Moeller A, Carlsen K-H, Sly PD, et al: Monitoring asthma in childhood: lung function, bronchial responsiveness and inflammation.

Eur Respir Rev. 2015;24:204-215.

COMMENT: In this interesting review, van Mastrigt and colleagues explore the literature regarding the use of exhaled breath condensate in pediatric pulmonary illnesses. They highlight a lack of standardization of collection methods and analysis techniques, which hampers the use of these tests in clinical practice. Clinicians, whether they are fans of exhaled nitric oxide or not, continue to hope for improved measures of inflammation. In this review, the authors identified over 1,100 papers on the topic. One thing is for sure, many more are to follow.

J.J.O.

van Mastrigt E, de Jongste JC, Pijnenburg MW: The analysis of volatile organic compounds in exhaled breath and biomarkers in exhaled breath condensate in children—clinical tools or scientific toys?

Clin Exp Allergy. 2015;45:1170-1188.

COMMENT: This is a wonderful review of the role of biomarkers in the treatment of asthma, specifically focusing on their role when considering the use of the new biologic agents.

J.J.O.

Hilvering B, Pavord ID: What goes up must come down: biomarkers and novel biologicals in severe asthma.

Clin Exp Allergy. 2015;45:1162-1169.

COMMENT: This rigorous review provides an overview of recent developments in mast cell biology, as well as diagnostic and therapeutic approaches to mast cell disorders.

C.D.

Theoharides TC, Valent P, Akin C: Mast cells, mastocytosis, and related disorders.

N Engl J Med. 2015;373:163-172.

COMMENT: Dr. Platts-Mills presents an excellent historical perspective of a variety of factors impacting the increasing prevalence of allergic diseases over the last two centuries. His conclusion that lifestyle changes are the most impactful factors contributing to the "allergy epidemic" is compelling. This should be a must-read for all allergists.

S.M.F.

Platts-Mills TAE: The allergy epidemics: 1870-2010.

J Allergy Clin Immunol. 2015;136:3-13.