Asthma linked with rhinosinusitis: An extensive review

Marianne Frieri, M.D., Ph.D.

ABSTRACT

Current literature related to asthma diagnosis, epidemiology, pathogenesis, and treatment linked with rhinosinusitis is important. Asthma is very heterogeneous; new theories and treatments are emerging. It is a growing epidemic among children and adults in the United States and the severity of asthma is caused by many factors such as lack of education, poor early recognition, decreased symptom awareness, improper medications, and phenotypic changes. Genetic variation, innate immune genes, those involved in tissue remodeling and arachidonic acid metabolism, and inflammatory mediators might contribute to the pathogenesis of chronic rhinosinusitis (CRS) linked with asthma. This extensive review addresses concepts of the burden of asthma and sinusitis, altered innate immunity, adaptive immunity, asthma remodeling, the airway epithelium, the role of airway smooth muscle cells, united allergic airway, genetics, an integral part in asthma, and CRS. In addition, the role of vitamin D in both asthma and CRS in the elderly and pediatric population, various treatment options, and exhaled nitric oxide are briefly addressed.

Asthma is a very complex disorder that involves the larger airways, but recent studies indicate that smaller airways play a key role in asthma exacerbation. Studies showed that individuals having more than two exacerbations per year have a higher degree of small airway dysfunction when compared with those with infrequent exacerbations. The National Asthma Education and Prevention Program defined asthma as a chronic disorder that involves airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. Racial/ethnic disparities in current asthma prevalence and medical care are a major public health concern. The differences in asthma prevalence and morbidity among major racial/ethnic populations in the United State were analyzed in the 2001–2010 National Health Interview Survey for adults (≥18 years old) and children and adolescents (<18 years old). Racial/ethnic differences in current asthma prevalence, asthma attacks, and increased use of emergency room visits for asthma among minorities persist among children and adults, and appropriate and effective asthma management and education may lead to better asthma control and reduce emergency care use.

The additional disease burden imparted by sinusitis and allergic rhinitis (AR) to patients with asthma was evaluated. Patients with asthma and sinusitis and those with asthma, sinusitis, and AR had more total health care visits and emergency room visits than did those with asthma alone. Thus, the additional disease burden of sinusitis on asthma is greater than that of AR, highlighting the importance of identifying comorbid diagnoses with asthma.

LINK WITH CHRONIC RHINOSINUSITIS AND BIOFILMS

The current prevalence of chronic rhinosinusitis (CRS) across various treatment settings to identify possible disparities in health care access and use between racial and ethnic populations was evaluated using survey database registries and extraction to identify the national prevalence of CRS in race/ethnic populations and resource use in ambulatory care settings. Thus, CRS is an important health condition for all major race/ethnic groups in the United States and significant differences may exist across racial and ethnic categories with regard to CRS health status and health care use.

Altered innate and adaptive immunity, tissue remodeling, and/or effects of microorganisms may play a role in the development of CRS with nasal polyps (CRSwNP) and its pathophysiology.

A down-regulation of epithelial innate immunity by maladaptive T helper cell type 2 (Th2) tissue inflammation has been established in patients with refractory CRSwNP. Maladaptive Th2 inflammation in the sinuses might negatively affect innate immunity in sinus mucosa by down-regulating Toll-like receptor 9 expression and a defect in innate immunity most commonly found in patients with refractory CRS is a decrease in lactoferrin levels in sinus secretions.

The adaptive immune responses that characterize Staphylococcus aureus biofilm-associated CRS, the relative contributions of staphylococcal superantigens, and...
S. aureus biofilms in the inflammatory makeup of this disease has been documented.7 S. aureus biofilms are associated with eosinophilic inflammation, across the spectrum of CRS, on the back of a Th2 skewing of the host's adaptive immune response, elevated eosinophilic cationic protein, and IL-5.7 Bacterial biofilms in CRS, S. aureus biofilms, and exotoxins that act as superantigens have been implicated in playing an important pathological role in the incidence, maintenance, and ongoing burden of CRS.8 A better understanding of the interplay between bacterial factors, host factors, and the environment will facilitate better management of this disease.9 Adaptive humoral immune responses in the airways are mediated by B cells and plasma cells that express highly evolved and specific receptors and produce immunoglobulins of most isotypes. A recent review discussed the generation, differentiation, signaling, activation, and recruitment pathways of B cells and plasma cells, with special emphasis on unique characteristics of subsets of these cells functioning within the respiratory system.9 Antigen exposure in the upper or lower airways can also drive expansion of B-lineage cells in the airway mucosal tissue and lead to the formation of inducible lymphoid follicles or aggregates that can mediate local immunity or disease.9

REMODELING IN ASTHMA AND CHRONIC SINUSITIS

Asthma pathophysiology involves airway inflammation, epithelial, smooth muscle dysfunction, and airway remodeling.10 Airway remodeling includes cellular proliferation, increased matrix protein deposition, basement membrane thickening, and angiogenesis.11 Alveolar epithelial cells may be more important in remodeling than bronchial epithelial cells.

Vascular endothelia growth factor (VEGF) secretion from allergen-stimulated alveolar epithelial cells and expression of cell-associated VEGF was shown.12 Derminatophagoides pteronyssinus is a common inhalant, indoor allergen, known for causing AR and airway inflammation. VEGF secretions from normal human lung fibroblasts and a dose-dependent fashion was shown to increase aggregation of human lung microvascular endothelial cells in response to transforming growth factor (TGF) β, in conditioned media from D. pteronyssinus (Der p1) with confluent alveolar epithelial cells.13 Detection of airway remodeling in subsets of asthma is difficult and clinically useful biomarkers are needed. A selected panel of cytokines, growth factors, fractional exhaled nitric oxide (FeNO), and possible radiographic imaging may assist clinicians in detecting and providing targeting therapy.14 A defect in barrier function and an impaired innate immune response to viral infection may provide the substrate on which allergic sensitization occurs. The repeated allergen exposure will lead to disease persistence that could also be used to explain airway wall remodeling and the susceptibility of the asthmatic lung to exacerbations.14 Asthma progression may be caused by persistent airway inflammation and/or impaired repair mechanisms. Allergen inhalation induces activation of Th2 cells, which express cytokines including IL-5, which generates TGF-β+ eosinophils that promote features of remodeling.

Chronic asthma is characterized by enhanced epithelial–mesenchymal communications with the release of a range of different growth factors linked to remodeling.15 The relative sensitivities of two markers of proliferation, proliferating cell nuclear antigen, and Ki-67, in airway smooth muscle, in vivo from subjects with moderate or severe asthma and healthy controls and in vitro was evaluated whether muscle remodeling is a dynamic process in asthma by quantifying the proliferation rate.16 Proliferating cell nuclear antigen was a highly sensitive marker of proliferation and heparin-binding epidermal growth factor was noted to be a potential biomarker during active remodeling of airway smooth muscle in severe asthma.16

Phenotypes of CRS can be differentiated based on mucosal remodeling and inflammatory patterns.17 CRS can be differentiated into several subgroups based on specific remodeling, inflammatory cell, and cytokine patterns.17 Current knowledge of factors that may predict asthma comorbidity in patients with CRS has confirmed that the same factors are also associated with severe asthma.17

TGF-β1 is a major participant in the airway remodeling of asthma, and enhanced epithelial immunoreactivity is known to occur in AR.18 D. pteronyssinus allergens from dialyzed standardized immunotherapy extract was shown to induce apoptosis and increase TGF-β1 secretion in confluent A549 cells treated with dialyzed D. pteronyssinus extract, which showed a four-fold increase in early apoptotic cells with a twofold increase in late apoptotic cells versus the control group, along with an increase of TGF-β1.18

TGF-β1 is known to play an important role in the tissue remodeling processes involved in CRS, with the biological functions of secreted TGF-β1 regulated by multiple proteins. The regulation of TGF-β1 activation and expression provides insight into the mechanism responsible for the different CRS subtypes, which will help further the investigation of novel therapy targets for the treatment.19

Fibrinolytic components, their receptors, and inhibitors are considered to play an important role in inflammation and tissue remodeling including CRS.20 TGF-β1 levels correlated with plasminogen activator inhibitor 1 in CRS without NPs.20 Fibrinolytic components were highly expressed in CRSwNP's compared with normal controls, whereas the inhibiting protein was up-regulated in CRS without NPs. Thus, correlations between
the expressions of fibrinolytic components and key mediators exist in CRS. Distinct remodeling patterns exist for different types of CRS, particularly for eosinophilic and noneosinophilic forms. TGF-β2 protein levels have been shown to be enhanced in CRS without NPs compared with CRSwNPs. Thus, tissue remodeling also associates with inflammation in CRS.

Mucosal remodeling in the sinuses is a recently described phenomenon in which the mucosa undergoes potentially irreversible changes as a result of ongoing underlying inflammatory processes. Research into remodeling that occurs in the bronchial airways in asthmatic patients has led to modification of asthma treatment guidelines and upper airway remodeling constitutes a new area of research that poses many unanswered clinical questions and may potentially alter the management of patients with severe CRS.

Human airway smooth muscle cells (ASMCs) can participate in linking inflammation with remodeling and associated genes. Inflammatory responses of ex vivo cultivated human ASMCs to TNF-α were evaluated by whole-genome microarray analyses and tested for inflammatory and remodeling genes for sensitivity to various agents. TNF-α induced the expression of 18 cytokines/chemokines and 5 tissue remodeling genes involved in severe/corticosteroid-insensitive asthma. Thus, human ASMCs and human bronchial epithelial cells participate in the interaction of inflammation and tissue remodeling. ASMCs, which proliferate and produce more chemokines in patients with severe asthma, exhibit corticosteroid insensitivity, as previously observed in macrophages and T cells. Cytokine expression of ASMCs in bronchial biopsy cultures from adults with nonsevere asthma and severe asthma and control subjects were compared in patients with severe asthma. ASMC TNF-α–induced phosphorylated p38 mitogen-activated protein kinase levels were increased, and suppression by dexamethasone of TNF-α–induced release of chemokines were reduced. Thus, a p38–mitogen-activated protein kinase inhibitor might have therapeutic benefit.

Asthma can result from bronchoconstriction to airways inflammation and remodeling. Omalizumab, a humanized anti-IgE monoclonal antibody, possesses anti-inflammatory activity by significantly reducing sputum and bronchial tissue eosinophilia compared with placebo, in addition to significant reductions in bronchial mucosal FcεRI, IgE+ cells, CD20+ B cells, CD3+, CD4+, and CD8+ T cells and cells staining for IL-4 compared with placebo. Additional studies showed the anti-inflammatory effects of omalizumab compared with budesonide on TNF-α, TGF-β, NO, and IL-4 markers of inflammation in human bronchial epithelial cells.

A chitinase-like protein as a possible biomarker of inflammation and airway remodeling was evaluated in severe pediatric asthma. The study included questionnaires, measurement of eNO in exhaled air, blood sampling for inflammatory biomarkers, and high-resolution computed tomography of the lungs to identify bronchial wall thickening.

GENETICS OF ASTHMA AND RHINOSINUSITIS

Gene environment interactions are important in the development of asthma and atopy. Asthma results from the combined interaction of genetic and environmental factors. Serum YKL-40 levels were measured and all asthmatic children were genotyped for a CHI3L1 promoter single-nucleotide polymorphism. YKL-40 levels were increased in children with severe, therapy-resistant asthma compared with healthy children, and they were also compared with children with controlled asthma after correction for genotype. An inherited or acquired epithelial susceptibility can occur to environmental agents, leading to induction of stress injury and repair. However, an alternative therapy of asthma pathogenesis has emphasized the importance of the airway microenvironment or the epithelial mesenchymal trophic unit. The expression of asthma is dependent on the inheritance of local susceptibility genes, which have the potential to interact with atopic predisposition, whereas inheritance of atopy can occur in the absence of atopy.

Asthma is a clinical heterogeneous condition and inflammatory mechanisms can contribute to variable results. Significant progress has been made identifying genetic polymorphisms that influence the efficacy and potential for adverse effects to asthma medications, including β2-adrenergic receptor agonists, corticosteroids, and leukotriene modifiers. Pharmacogenetics holds great promise to maximize clinical outcomes and minimize adverse effects. Genome-wide association studies have begun to identify genes underlying asthma (e.g., IL1RL1), which represent future therapeutic targets. Pharmacogenetics of current asthma therapies was reviewed and discussed the genetics underlying selected phase II and future targets. There has been good progress in recent years in asthma susceptibility gene discovery, driven mainly by genome-wide association approaches that investigate up to 1 million single-nucleotide polymorphisms in large populations composed of thousands of individuals. Many susceptibility genes are identified using this approach. Advances in adult asthma diagnosis and treatment in 2012 was reviewed, stating their potential therapeutics and gene–environment interactions. There was also debate on the effect of the environment on an individual’s health from pollution, climate change, and epigenetic influences. These data underlined the importance of
understanding gene–environment interactions in the pathogenesis of asthma and response to treatment.31

Current literature regarding the genetics of CRS in a comprehensive fashion including genes involved in antigen presentation, innate and adaptive immune responses, tissue remodeling, and arachidonic acid metabolism was reviewed.32 Studies suggest that genetic variation in the cystic fibrosis transmembrane conductance regulator gene, HLA genes, innate immune genes, inflammatory mediators including IL-13 and IL-33, and genes involved in tissue remodeling and arachidonic acid metabolism might contribute to the pathogenesis of CRS.32 This review stated that one could be able to glean relevant information from genetic studies of related diseases of the airway, both in terms of methodological approaches and in terms of candidate genes implicated in other airway pathology.32

UNITED AIRWAY CONCEPT AND LINK
WITH CRS

Recent advances in AR, CRS, and asthma to understand the upper and lower airway as one system was reviewed. Excess mucosal inflammation with immune dysregulation is a common feature of AR, CRS, and asthma and an important role for innate immunity is now apparent and offers prospects of novel therapeutic approaches in the future.33 The united allergic airway is a theory that connects AR, CRS, and asthma, viewed as arising from a common atopic entity.34 Thus, AR, asthma, and CRS are linked by the united allergic airway, a notion that encompasses commonalities in pathophysiology, epidemiology, and treatment.34 The aggregation of research suggests that AR and asthma are, in fact, one syndrome in two parts of the respiratory tract, supported pathophysiologically, epidemiologically, and through numerous clinical studies. Being afflicted with AR is often the harbinger of asthma at a future date.34 The etiology for the connection between asthma and AR is likely multifactorial. Although nasal blockage and aspiration of nasal contents have long been accepted as contributing factors, there is a growing body of evidence that suggests that a systemic response plays an important role in the AR–asthma relationship.34

Patients with sinusitis should be evaluated for a possible concomitant asthma and patients with asthma should always be evaluated for possible nasal disease. Physicians should always keep these notions in mind and evaluate and treat respiratory diseases taking into account the unity of the respiratory tract.37

ROLE OF VITAMIN D IN ASTHMA
AND SINUSITIS

Vitamin D is also capable of inducing the expression of several anti-infective molecules, such as cathelicidin. Thus, Vitamin D has a number of biological effects that are likely important in regulating key mechanisms in asthma.38 The relationship between Vitamin D, asthma disease severity, and airway remodeling in asthmatics patients was evaluated.39 Lower vitamin D levels in children with severe, therapy-resistant asthma were associated with increased airway smooth muscle mass and worse asthma control and lung function. The link between vitamin D and airway structure and function suggests vitamin D supplementation may be useful in the pediatric population.39

Vitamin D supplementation may lead to improved asthma control by inhibiting the influx of inflammatory cytokines in the lung and increasing the secretion of IL-10 by T-regulatory cells and dendritic cells.39 Recent findings on the function of vitamin D may also explain aspects of the pathophysiology of CRS and may help direct future interventions and treatment of these diseases.41

Vitamin D3 insufficiency/deficiency is common in CRSwNP patients, especially in those of African American race, and lower levels of vitamin D3 are associated with worse Lund-Mackay scoring on computed tomography scans.42 The role of vitamin D3 in CRSwNP warrants additional investigation.42

ASTHMA AND CRS IN ELDERLY PATIENTS

Asthma is associated with significant morbidity and mortality in the geriatric population.43 Despite the ris-
ing incidence of asthma in people >65 years of age, the diagnosis is frequently missed in this population. Factors that contribute to this include age-related changes to the respiratory and immune systems, lack of symptoms, clinician unawareness, and lack of evidence-based guidelines for diagnosis and management that target this population. A multidiscipline approach is needed to better manage these patients and a broad set of goals is needed to guide future management of this growing population. The presence of atopy in patients failing medical therapy for both types of CRS was examined. The objective of this research was to analyze the frequency and distribution of allergen sensitivity in patients failing medical therapy for CRS with and without NPs and CRS without NPs in comparison with rhinitis patients without CRS and the general population. Compared with control subjects and patients without NPs those with NPs were older and more likely to be men.

**ASTHMA AND CRS IN THE PEDIATRIC POPULATION**

Asthma prevalence in the pediatric population has been on a steady increase since 2008. Early risks to decrease exposure to harmful conditions in the environment can trigger asthma which may not be clinically evident in children until they reach adulthood. A retrospective literature review on the prevalence of asthma in the urban environment versus the rural environment was evaluated to understand the effect of the environment on asthma. Obesity has been associated with asthma in patients from an underserved low physician-to-patient ratio and a minimal difference in the prevalence of asthma in the urban and rural environment in pediatric patients was reported. New clinical studies, especially in childhood asthma, suggest that inflammation and remodeling occur independently of each other and maybe occur in parallel, and that airway wall remodeling, especially of the airway smooth muscle, occurs before any signs of inflammation can be found.

Five to 13% of upper respiratory tract infections in children develop into acute rhinosinusitis and although not life-threatening, it profoundly affects the child’s school performance and sleep patterns and if untreated, it could progress to CRS. Rhinosinusitis is an upper airway infection with chronic implications and prompt management of acute cases would prevent cases from slipping into chronicity with resistant polymicrobial infections. Management of CRS is an expensive, long-term affair with high likelihood of complications. Hence, prevention and control of rhinosinusitis will assist in decreasing morbidity and lessen the burden on health care expenditure. Achieving sinonasal eutrophism and efficient mucociliary transport is important to sinus health and reduction of recurrences.

**FeNO, ASTHMA, AND CRS PHENOTYPES**

Recent efforts to classify subphenotypes of asthma have focused on sputum cellular inflammation profiles, cluster analyses of clinical variables, and molecular and genetic signatures. Researchers and clinicians can now evaluate biomarkers of Th2-driven airway inflammation in asthmatic patients, such as serum IgE levels, sputum eosinophil counts, FeNO, and serum periostin levels. These markers can aid decision making in clinical trials and drug development and identify subsets of patients who might benefit. It is unlikely that these therapies will benefit all asthmatic patients; however, there are advances in understanding asthma subphenotypes in relation to clinical variables and Th2 cytokine responses. These subphenotypes offer the opportunity to improve the efficacy and safety of proposed therapies for asthma.

Both pendrin and periostin in AR and CRS suggests that pendrin can induce mucus production and perios tin can induce tissue fibrosis and remodeling in the nasal mucosa. Therefore, these mediators may be therapeutic target candidates for AR, CRSwNPs, and aspirin-induced asthma.

FeNO, peripheral blood eosinophil, periostin, YKL-40, and IgE levels were measured and compared biomarkers with airway eosinophilia in asthmatic patients. FeNO levels and serum periostin levels in 59 patients with severe asthma showed that of these indices the serum periostin level was the single best predictor of airway eosinophilia. Thus, periostin is a systemic biomarker of airway eosinophilia in asthmatic patients and has potential usefulness in patient selection for emerging asthma therapeutics targeting Th2 inflammation.

Recent evidence indicates that FeNO identifies Th2-mediated airway inflammation with a high positive and negative predictive value for identifying corticosteroid responsive airway inflammation. Evidence for FeNO as a predictor of Th2-mediated inhaled corticosteroid (ICS) responsive airway inflammation was reviewed and recent studies evaluated the role of FeNO, determining whether it was helpful or not, in the assessment and management of pediatric asthma. The article stated that FeNO may be useful in identifying patients at risk for future impairment or loss of asthma control during reduction/cessation of ICS treatment and FeNO testing has an important role in the assessment of pediatric patients with suspected asthma and in the management of pediatric patients with established asthma.

The alveolar fraction of eNO (C_{alv}NO) in patients with mild asthma with different levels of control of symptoms and a significant correlation was found between the Asthma Control Test (ACT) score and C_{alv}NO, which was significantly higher in patients with uncon-
trolled asthma than in patients with controlled/partially controlled asthma. The alveolar component of eNO was associated with the lack of asthma control in patients with mild, untreated asthma. This article stated that this observation supports the notion that abnormalities of the peripheral airways are implicated in the mildest forms of asthma.

FeNO is most accurately classified as a marker of Th2-mediated airway inflammation with a high positive and negative predictive value for identifying corticosteroid-responsive airway inflammation. Results of a meta-analysis of three adult studies comparing asthma exacerbation rates with FeNO-based versus clinically based asthma management algorithms, one of which was not included in a 2012 Cochrane meta-analysis, stated that FeNO has value for identifying patients with airway inflammation who will and will not respond to corticosteroids and the use of FeNO in conjunction with clinical parameters is associated with significantly lower asthma exacerbation rates compared with asthma managed using clinical parameters alone. Thus, these data indicate that FeNO testing has an important role in the assessment and management of adult asthma and further studies will continue to define the exact role of FeNO testing in adult asthma.

Decreased FeNO levels after a targeted educational intervention in Hispanic and African American adult asthmatic patients was recently reported. FeNO mean change score significantly differed ($p = 0.049$) between the treatment and control groups, with a larger mean change score for the treatment group. A targeted educational intervention was studied to verify if it would have greater benefits for adult asthma patients than standard education for our primary outcome of FeNO, and a secondary outcome of the ACT score was evaluated. However, there was no significant difference for ACT mean change scores between the treatment and control groups. Small airways dysfunction was reviewed and showed an association between worsening asthma control, higher numbers of asthma exacerbations, the presence of nocturnal asthma, more severe bronchial hyperresponsiveness, exercise-induced asthma, and the late-phase allergic response. Early recognition of small airways dysfunction is important for both the patient and the physician, allowing for faster treatment targeted toward the small airways.

**ASTHMA AND RHINOSINUSITIS PHENOTYPES**

The clinical phenotype of asthma as notoriously heterogeneous, affected by genetic and environmental exposures in addition to interactions between airway structural cells including epithelial cells, and the immune system, and contributions from cells other than Th2 cells was discussed. This complex interplay has made it increasingly apparent that immune responses are tailored to the individual patient and determined by the weight of each influence, and thus asthma as a Th2 disease is too conservative but is an important concept that needs to be addressed, in animal models and clinically, is that of T-cell plasticity and how lymphocytic responses are determined by environmental influences.

Both genetics and phenotyping in chronic sinusitis with a focus on recognized distinct presentations of chronic sinus disease including distinguishing clinical presentations, cellular and molecular characteristics, genetic differences, and current treatment options was discussed.

The diverse CRS phenotypes using cluster analysis was investigated. CRS was classified into four phenotypes based on NPs and mucosal eosinophil counts. Cutoff points for these factors were identified by tree analysis. Glandular mast cells with distinct phenotypes in CRSwNPsw&sw were evaluated. This study showed a unique localization of mast cells within the glandular epithelium of NPs and showed that mast cells in NPs have distinct phenotypes that vary by tissue location. Thus, glandular mast cells and the diverse subsets of mast cells detected may contribute to the pathogenesis of CRSwNPsw.

**TREATMENT OF ASTHMA AND CRS**

There is a vast range of medications for asthma and CRS by the general practitioner and in consultation with the specialist. Asthma medications involve $\beta$-agonists, leukotrienes, ICSs, combination medications involving $\beta$-agonists and ICS, and omalizumab approved for patients with moderate-to-severe allergic asthma who fail corticosteroid therapy. The use of omalizumab was studied in 4308 patients and 38% had a reduction in asthma exacerbation and 47% had fewer emergency room visits. Interim data from the EXCELS study published in 2012 showed that patients with omalizumab therapy experienced improvement in asthma control, which was maintained during 2 years of longitudinal follow-up.

Many patients desire the use of nonpharmacologic agents for symptom relief and thus many studies are focusing on this practice of medicine. A knowledge translation framework to implement asthma clinical practice guidelines in a multistep approach was described by the Canadian Institutes of Health Research System. A regional administrative infrastructure and interdisciplinary care teams were developed and six guideline-based care elements were implemented, including spirometry measurement, asthma controller therapy, a written self-management action plan, and general asthma education, including the inhaler device technique, role of medications, and environmental control strategies. A recent study indicated that chest
physiotherapy may improve quality of life, cardiopulmonary fitness, and inspiratory pressure and reduce symptoms and medication usage. Adding a comprehensive lifestyle modification program to standard medical management can offer greater clinical benefit than standard management alone. Increasing interventions that account for literacy might improve asthma outcomes but larger studies need to be completed in the United States to prove effectiveness among its patient populations.

Several promising therapies for asthma that target the IL-13/IL-4 signal transducer and activator of transcription 6 pathway are in development, including anti–IL-13 monoclonal antibodies and IL-4 receptor antagonists. The efficacy of these new potential asthma therapies depends on patient responsiveness and an understanding of how IL-13–directed therapies might benefit asthmatic patients.

Dupilumab, a fully human monoclonal antibody to the α-subunit of the IL-4 receptor, in patients with persistent, moderate-to-severe asthma and elevated eosinophil levels was recently evaluated. In these patients with elevated eosinophil levels who used inhaled glucocorticoids and long-acting β2-agonists, dupilumab therapy, when compared with placebo, was associated with fewer asthma exacerbations when long-acting β2-agonists and inhaled glucocorticoids were withdrawn, with improved lung function and reduced levels of Th2-associated inflammatory markers.

Several new blockers of specific mediators, including prostaglandin D2, IL-5, IL-9, and IL-13, are in clinical trials that might benefit patients with subtypes of severe asthma, and several broad-spectrum anti-inflammatory therapies that target neutrophilic inflammation are in clinical development. Several subtypes of severe asthma are now recognized, and in the future, it will be necessary to find biomarkers that predict responses to specific forms of therapy.

Anti–TNF-α is a potential target for treatment of severe asthma. However, controlled studies have shown controversial results and the risk–benefit profile of TNF-blocking agents is still debated. A recent case series suggested that anti–TNF-α therapy may improve the condition of a subgroup of patients with severe steroid–refractory asthma with a favorable risk–benefit profile. However, specific controlled trials of this subgroup are warranted.

Literature supports the implementation of aggressive medical management as the mainstay of therapy for CRS. Scientific literature exists for the use of intranasal and systemic corticosteroids, antibiotics, nasal saline lavages, and unique therapies for individuals both with and without NPs. There are also promising new biological therapies on the horizon with mepolizumab and omalizumab and treatment with aggressive medical management can potentially postpone the need for surgical intervention.

Clinicians should use intranasal corticosteroids and nasal saline lavages as maintenance therapy and systemic corticosteroids and antibiotics should be used for acute exacerbations, especially in individuals with NPs.

There is no high-level evidence to support the use of oral antibiotics in CRS. Placebo-controlled studies of macrolide antibiotics indicate either no effect or limited degrees of improvement. Recent literature has identified that sinusitis refractory to medical therapy may represent an odontogenic source, and this should be addressed by dental surgery rather than by additional antibiotics. Oral antibiotics can be prescribed most confidently for the management of CRS when purulent exacerbations of disease are detected endoscopically and antibiotic choices are directed by culture. Long-term macrolide antibiotic therapy, acting through immunomodulatory pathways, may be of benefit in CRS patients with low IgE levels.

Functional endoscopic sinus surgery (ESS) has been shown to improve sinus-related symptoms and quality of life in children with CRS.

This study evaluated 1-year outcomes in patients with CRS who were considered surgical candidates by study criteria and elected either medical management or ESS. In addition, some patients initially enrolled in the medical treatment arm crossed over to the surgery arm during the study period and their respective outcomes were evaluated. With 1 year of follow-up, patients electing ESS experienced significantly higher levels of improvement in outcomes compared with patients managed by medication alone. In addition, a crossover cohort who initially elected medical management experienced improvement in several outcomes after crossing over to ESS.

In conclusion, this study has extensively reviewed the link with CRS and biofilms; remodeling in asthma and chronic sinusitis; genetics of asthma and rhinosinusitis; the united airway concept and link with CRS; the role of vitamin D in asthma and sinusitis; asthma and CRS in the elderly and pediatric population; FeNO, asthma, and CRS phenotypes; and the treatment of asthma and CRS.

REFERENCES

1. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma- summary report. J Allergy Clin Immunol 120(suppl):S94–S138, 2007.
2. Oraka E, Iqbal S, Flanders WD, et al. Racial and ethnic disparities in current asthma and emergency department visits: Findings from the National Health Interview Survey, 2001–2010. J Asthma 50:488–496, 2013.

3. Bhattacharyya N, and Kepnes LJ. Additional disease burden from hay fever and sinusitis accompanying asthma. Ann Otol Rhinol Laryngol 118:651–655, 2009.

4. Soler ZM, Mace JC, Litvack JR, and Smith TL. Chronic rhinosinusitis, race, and ethnicity. Am J Rhinol Allergy 26:110–116, 2012.

5. Hsu J, and Peters AT. Pathophysiology of chronic rhinosinusitis with nasal polypl. Am J Rhinol Allergy 25:285–290, 2011.

6. Hamilos DL. Host-microbial interactions in patients with chronic rhinosinusitis. J Allergy Clin Immunol 131:1263–1264, 1264.e1–6, 2013.

7. Foreman A, Holtappels G, Psaltis AJ, et al. Adaptive immune responses in *Staphylococcus aureus* biofilm-associated chronic rhinosinusitis. Allergy 66:1449–1456, 2011.

8. Madeo J, and Frieri M. Bacterial biofilms and chronic rhinosinusitis. Allergy Asthma Proc 34:335–341, 2013.

9. Kato A, Hulse KE, Tan BK, and Schleimer RP. B-lymphocyte lineage cells and the respiratory system. J Allergy Clin Immunol 131:933–957, 2013.

10. Frieri M. Asthma concepts in the new millennium: Update in asthma pathophysiology. Allergy Asthma Proc 26:83–88, 2005.

11. Frieri M. Advances in the understanding of allergic asthma. Allergy Asthma Proc 28:614–619, 2007.

12. Capetandes A, Haque FN, and Frieri M. Confluent human pulmonary type II epithelial cells (A549) cells express cytoplasmic VEGF. J Invest Med. 36:7, 2004.

13. Capetandes A, Horne NS, and Frieri M. *Dermatophagoides pteronyssinus* extract-treated confluent type II epithelial cells (cA549) and human lung mesenchymal cell growth. Ann Allergy Asthma Immunol 95:381–388, 2005.

14. Holgate ST, Arshad HS, Roberts GC, et al. A new look at the pathogenesis of asthma. Clin Sci (Lond) 118:439–450, 2009.

15. Broide DH. Immunologic and inflammatory mechanisms that drive asthma progression to remodeling. J Allergy Clin Immunol 121:560–570, 2008.

16. Hassan M, Jo T, Risse PA, et al. Airway smooth muscle remodeling is a dynamic process in severe long-standing asthma. J Allergy Clin Immunol 125:1037–1045.e3, 2010.

17. Bachert C, and Zhang N. Chronic rhinosinusitis and asthma: Novel understanding of the role of IgE “above atopy.” J Intern Med 272:133–143.2012.

18. Frisella PD, Silverberg J, Joks R, and Frieri M. Transforming growth factor-beta. A role in the upper airway and rhinosinusitis-D. *pterygossinus*-induced apoptosis with pulmonary alveolar cells. Am J Rhinol Allergy 25:231–235, 2011.

19. Kou W, Hu GH, Yao HB, et al. Regulation of transforming growth factor-beta activation and expression in the tissue remodeling involved in chronic rhinosinusitis. J ORL Otorhinolaryngol Relat Spec 74:172–178, 2012.

20. Sejima T, Holtappels G, and Bachert C. The expression of fibrinolytic components in chronic paranasal sinus disease. Am J Rhinol Allergy 25:1–6, 2011.

21. Shi LL, Xiong P, Zhang L, et al. Features of airway remodeling in different types of Chinese chronic rhinosinusitis are associated with inflammation patterns. Allergy 68:101–109, 2013.

22. Bassiouini A, Naidoo Y, and Wormald PJ. Does mucosal remodeling in chronic rhinosinusitis result in irreversible mucosal disease? Laryngoscope 122:225–229, 2012.

23. Knobloch J, Lin Y, Konradi J, et al. Inflammatory responses of airway smooth muscle cells and effects of endothelin receptor antagonism. Am J Respir Cell Mol Biol 49:114–127, 2013.

24. Chang PJ, Bhavsar PK, Michaeloudes C, et al. Corticosteroid insensitivity of chemokine expression in airway smooth muscle of patients with severe asthma. J Allergy Clin Immunol 130:877–885.e5, 2012.

25. Bousquet J, Jeffery PK, Busse WW, et al. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 161:1720–1745, 2000.

26. Djukanovic R, Wilson SJ, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med 1120:583–593, 2004.

27. Huang YC, Leyko B, and Frieri M. Effects of omalizumab and budesonide on markers of inflammation in human bronchial epithelial cells. Ann Allergy Asthma Immunol 95:443–451, 2005.

28. Konradsen JR, James A, Nordlund B, et al. The chitinase-like protein YKL-40: A possible biomarker of inflammation and airway remodeling in severe pediatric asthma. J Allergy Clin Immunol 132:328–335.e5, 2013.

29. Davies DE, Wicks J, Powell RM, et al. Airway remodeling in asthma: New insights. J Allergy Clin Immunol 111:215–225, 2003.

30. Portelli M, and Sayers I. Genetic basis for personalized medicine in asthma, Expert Rev Respir Med 6:223–236, 2012.

31. Apter A. Advances in adult asthma diagnosis and treatment in 2012: Potential therapeutics and gene-environment interactions. J Allergy Clin Immunol 131:47–54, 2013.

32. Hsu J, Avila PC, Kern RC, et al. Genetics of chronic rhinosinusitis: State of the field and directions forward. J Allergy Clin Immunol 131:977–993, 2013.

33. Kariyawasam HH, and Rotiroti G. Allergic rhinitis, chronic rhinosinusitis, and asthma: Unravelling a complex relationship. Curr Opin Otolaryngol Head Neck Surg 21:79–86, 2013.

34. Feng CH, Miller MD, and Simon RA. The united allergic airway: Connections between allergic rhinitis, asthma, and chronic sinusitis. Am J Rhinol Allergy 26:187–190, 2012.

35. Caimmi D, Marseglia A, Pieri G, et al. Nose and lungs: One allergic disorders and immune mechanisms. Allergy Asthma Proc 34:427–433, 2013.

36. Suzuki H, Watanabe S, and Pawankar R. Rhinosinusitis and asthma-microbiome and new perspectives. Curr Opin Allergy Clin Immunol 13:45–49, 2013.

37. Ciprandi G, Caimmi D, Miraglia Del Giudice M, et al. Recent developments in united airways disease. Allergy Asthma Immunol Res 4:171–177, 2012.

38. Frieri M, and Vallurri A. Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms. Allergy Asthma Proc 32:438–444, 2011.

39. Gupta A, Sjoukes A, Richards D, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. Am J Respir Crit Care Med 184:1342–1349, 2011.

40. Sandhu MS, and Casale TB. The role of vitamin D in asthma. Ann Allergy Asthma Immunol 105:191–199, 2010.

41. Akbar NA, and Zacharek MA. Vitamin D: Immunomodulation of asthma, allergic rhinitis, and chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg 19:224–228, 2011.

42. Schlosser RJ, Soler ZM, Schmedes GW, et al. Impact of vitamin D deficiency upon clinical presentation in nasal polyposis. Int Forum Allergy Rhinol 4:196–199, 2014.

43. Madeo J, Li Zhenhong, and Frieri M. Asthma in the geriatric population. Allergy Asthma Proc 34:427–433, 2013.

44. Tan BK, Zirkle W, Chandra RK, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. J Allergy Clin Immunol Res 4:171–177, 2012.

45. Malik H, Kumar K, and Frieri M. Minimal difference in the prevalence of asthma in the urban and rural environment. Clin Med Insights Pediatr 6:33–39, 2012.

46. Malik H, Kumar K, Fogel J, and Frieri M. Obesity is associated with asthma in patients from an underserved low physician to
mvement on airway remodeling in asthma. N Engl J Med 364:2006–2011.

50. James AL, Elliot JG, Jones RL, et al. Airway smooth muscle hypertrophy and hyperplasia in asthma. Am J Respir Crit Care Med 185:1058–1064, 2012.

51. O’Reilly R, Ullmann N, Irving S, et al. Increased airway smooth muscle in preschool wheezers who have asthma at school age. J Allergy Clin Immunol 131:1024–1032, 1032.e1–6, 2013.

52. Shahid SK. Rhinosinusitis in children. ISRN Otolaryngol 851831:2012, 2012.

53. Ingram JL, and Kraft M. IL-13 in asthma and allergic disease: Asthma phenotypes and targeted therapies. J Allergy Clin Immunol 130:829–842, 2012.

54. Ishida A, Ohta N, Suzuki Y, et al Expression of pendrin and periostin in allergic rhinitis and chronic rhinosinusitis. Allergol Int 61:589–595, 2012.

55. Jia G, Erickson RW, Choy DF, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol 130:647–654.e10, 2012.

56. Mahr TA, Malka J, and Spahn JD. Inflammometry in pediatric asthma: A review of fractional exhaled nitric oxide in clinical practice. Allergy Asthma Proc 34:210–219, 2013.

57. Scichilone N, Battaglia S, Taormina S, et al. Alveolar nitric oxide biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol 131:1513–1517, 2013.

58. Donohue JP, and Jain N. Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. Respir Med 107:943–952, 2013.

59. Patel R, Fogel J, Zitt M, and Frieri M. Decreased exhaled nitric oxide levels after a targeted educational intervention in Hispanic and African American adult asthmatics: A preliminary study. 2013.

60. van der Wiel E, ten Hacken NH, Postma DS, and van den Berge M. Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. J Allergy Clin Immunol 131:646–657, 2013.

61. Lloyd CM, and Saglani S. T cells in asthma: Influences of genetic, environment, and T-cell plasticity. J Allergy Clin Immunol 131:1267–1274, 2013.

62. Payne SC, Borish L, and Steinke JW. Genetics and phenotyping in chronic sinusitis. J Allergy Clin Immunol 128:710–720, 2011.

63. Nakayama T, Asaka D, Yoshikawa M, et al. Identification of chronic rhinosinusitis phenotypes using cluster analysis. Am J Rhinol Allergy 26:172–176, 2012.

64. Takabayashi T, Kato A, Peters AT, et al. Glandular mast cells with distinct phenotype are highly elevated in chronic rhinosinusitis with nasal polypos. J Allergy Clin Immunol 130:410–420.e5, 2012.

65. Eisner MD, Zazzali JL, Miller MK, et al. Longitudinal changes in asthma control with omalizumab: 2-Year interim data from the EXCELS study. J Asthma 49:642–648, 2012.

66. Pokladnikova J, and Selke-Krulichova I. Effectiveness of a comprehensive lifestyle modification program for asthma patients: A randomized controlled pilot trial. J Asthma. 50: 318–326, 2013.

67. Taille C, Poulet C, Marchand-Adam S, et al. Monoclonal antibodies for severe steroid-dependent asthma: A case series. J Pediatr 165:1077–1082, 2014.

68. Vlastarakos PV, Fetta M, Segas JV, et al. Functional endoscopic sinus surgery improves sinus-related symptoms and quality of life in children with chronic rhinosinusitis: A systematic analysis and meta-analysis of published interventional studies. Clin Otolaryngol (Phila) 52:1091–1097, 2013.