Polyps, asthma, and allergy: what's new

Dimitrios Terzakis[a] *and Christos Georgalas*[b,c]

Purpose of review
Although chronic rhinosinusitis with nasal polyps, asthma, and allergy share common inflammatory mechanisms, there is no evidence of cause-and-effect relationship. In this review, we present new studies investigating the complex immunology that links these diseases. Advances in new therapies as well as evidence regarding indication and timing of surgery, especially of more complex cases, are highlighted.

Recent findings
New studies have endotyped patients in an effort to describe the exact inflammatory profile of each phenotype, whereas described cytokines seem to play a significant role in amplification of T2 inflammation, directly or via innate lymphoid cells. New mAbs that block specific cytokines of these pathways have been developed and seem to show reduced asthma severity as well as improved sinonasal outcomes. Moreover, it has been shown that operating early in the course of disease leads not only to bigger improvements in SNOT-22 outcomes but also to reduced asthma incidence postoperatively in refractory cases.

Summary
Applying data from current studies in clinical practice, we could better manage refractory cases with asthma and polyps, both medically and surgically. Treatment has to be patient-centered, and this demands a multidisciplinary-team approach of the airway diseases.

Keywords
allergy, asthma, interleukins, nasal polyps

INTRODUCTION: PHENOTYPING AND ENDOTYPING CRSwNP

Chronic rhinosinusitis (CRS) is a very common disease, affecting more than 10% of adult population with a significant socioeconomic burden and impairment in general quality of life [1,2].

CRS is traditionally divided into two cardinal forms, chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP), with the latter encompassing more than one subtype including allergic fungal rhinosinusitis (AFRS) and aspirin-exacerbated respiratory disease (AERD). AERD is considered as a refractory subtype of CRSwNP and is covered in another review of this issue.

Although CRSwNP is considered a single entity, significant effort has been invested in research attempting to understand the complex immunology of CRS and identify the inflammatory profiles (endotypes), which produce the diverse clinical features (phenotypes). In a recent study, Tomassen *et al.* [3▪▪] identified 10 different endotypes by using cluster analysis of biomarkers and subsequently tried to correlate them with phenotypes. He confirmed what was already known, that CRSsNP is predominantly Th1 and CRSwNP Th2-cell mediated, but also concluded that inflammation in patients with CRS is more diverse than previously thought. Polyps' phenotype was associated with more than seven different endotypes, but each one of them was associated with a different incidence of polyps and comorbid asthma implying that a more complex inflammatory pattern was at play, accounting for similar clinical symptoms.

Endotyping patients could be the key to better understand the underlying pathophysiology of nasal polyps and their association with allergy and asthma and to develop biologics targeting specific inflammatory pathways, leading to an individualized, patient-tailored therapy.

[a]Department of Otorhinolaryngology, Henry Dunant Hospital, Athens, [b]Endoscopic Skull Base Center, Hygeia Hospital, Marousi, Greece and [c]Center for Skull Base Patients, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to Christos Georgalas, PhD, FRCS (ORL-HNS), Endoscopic Skull Base Center, Hygeia Hospital, Marousi, Greece.
Tel: +0030 6981084101; e-mail: cgeorgalas@gmail.com

Curr Opin Otolaryngol Head Neck Surg 2017, 25:12–18
DOI:10.1097/MOO.0000000000000323

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

KEY POINTS

- Endotyping patients will allow us to understand the complex immunology that allergy, asthma, and polyps share and help us develop therapeutic strategies based on pathomechanism.
- Newly described cytokines (IL-25/IL-33) and receptors on Th2 cells provide possible mechanisms of amplification of inflammation and a new field of developing drugs for specific immune targets.
- Screening tests and management of allergy and asthma should be considered in CRSwNP patients as it seems to optimize the medical therapy.
- New mAbs already used in eosinophilic asthma reduce polyp size and improve sinonasal outcomes in new studies by targeting common pathways of Th2 inflammation.
- ESS reduces the incidence of asthma postoperatively, and patients who were operated early demonstrated greater reduction.

ALLERGY AND ASTHMA: CAUSATION OR CONTRIBUTING FACTORS

Allergy

The role of atopy in polyp formation is controversial. Although a cause-and-effect relationship between allergic rhinitis and CRS has been long proposed, this was based on evidence derived mainly from epidemiological studies characterized from heterogeneity of design, inclusion criteria, population, and allergens studied. Most of these studies lumped together patients with CRSsNP with nasal polyp patients, whereas the criteria used for CRS diagnosis were often inappropriate.

Applying the revised Bradford Hill criteria for causation [4], it was impossible to prove any link between CRS and allergy (Table 1). If we exclude studies dealing with CRSsNP patients, the available evidence for and against a link between allergy and nasal polyp is summarized in Table 2.

However, that is not to say that allergy is not a disease-modifying factor in CRS: in the same study [4], the authors report that the presence of elevated IgE in nonatopic patients and activation of mast cells and eosinophils directly by local microorganisms without IgE mediation could explain the variable clinical effects of allergen avoidance, allergen immunotherapy, systemic and topical antibiotic and antifungal treatment without allergy being the intermediary mechanism. The compelling notion of the 'unified airway' does not necessarily imply a route leading from allergy to the development of sinusitis but rather a common pathway. Similar conclusions regarding the quality and paucity of evidence for such a link are reached in another evidence-based review assessing the relationship between allergy and CRSwNP [22]. Exception to that is AFRS, a more severe form of CRSwNP, in which type I hypersensitivity and IgE specific to fungi is one of the diagnostic criteria as described from Bent and Kuhn [23].

The most recent International Consensus Statement on Allergy and Rhinology: Rhinosinusitis [24▪] also embraces the above by stating that inhalant allergy may be a disease-modifying factor in CRSwNP, but evidence for a direct cause–effect relationship is lacking.

Asthma

Asthma appears to be more prevalent in CRSwNP patients and vice versa, and the majority of publications show an association between them expressing the unified airway concept [25]. However, they are not always clinically present together, and a recent study shows that lower airway dysfunction is common in CRSwNP but does not correlate to the severity of nasal disease [26]. Moreover, patients with nasal polyps appear to have late-onset, nonatopic asthma [27], and patients with both diseases seem to have a worse disease course with higher Lund–Mackay score and more severe nasal obstruction and hyposmia [28]. Interestingly, patients with persistent asthma and CRSwNP have an accumulative impact on the loss of smell [29].

A study published this year showed that allergic rhinitis is a significant risk factor for asthma. Patients with CRS examined retrospectively, and the yearly incidence of patients with new asthma diagnoses was significantly greater in the group of patients with allergic rhinitis [30▪▪].

Pathophysiology

Speaking from a pathophysiology point of view, what seems to link atopy, asthma, and polyps are common inflammatory pathways such as mainly Th2 cell-mediated response, elevated IgE, eosinophilic inflammation, and also mast cells and basophils. Cytokines produced by Th2 cells are mainly IL-4 (responsible for B-cell activation and IgE synthesis), IL-5 (development and survival of eosinophils), and IL-13.

The role of IgE is not clear. Patients with negative allergy tests and not obvious aeroallergen sensitization benefit from omalizumab, an IgE binding antibody. This anti-IgE strategy has shown promising therapeutic potential in nonatopic patients with polyps and asthma and indicates that IgE may have

1068-9508 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Table 1. Applying the revised Bradford Hill guidelines on the evidence in favor and against of allergy being a predisposing factor for chronic rhinosinusitis

Evidence regarding causal association between allergy and CRS based on revised Bradford Hill criteria (guidelines)		
	Size of effect not attributable to plausible confounding (experiment)	There is possible selection or referral bias, as physicians involved also have an interest in allergy
		More data are required from large epidemiological studies that utilize explicit criteria
Direct	Appropriate temporal and/or spatial proximity (cause precedes effect and effect occurs after a plausible interval; cause occurs at the same site as the intervention) (strength)	No increase of CRS during pollen season
		Animal studies are mainly for ARS
	Dose-responsiveness and reversibility (temporality)	Difficult to estimate the impact of AR severity on CRS, as more serious cases can be considered SCUAD
		Conflicting evidence on the role of allergy treatment on CRS and FESS
Mechanistic	Evidence for a mechanism of action (biological, chemical, and mechanical) (biological gradient and biological plausibility)	The hypothesis that allergic inflammation can cause chronic obstruction of osteomeatal complex is rational. However, the pathophysiology of CRS is unknown
	Coherence (coherence)	AFRS by definition is related to allergy
Parallel	Replicability (consistency)	Inconsistent nomenclature and diagnostic criteria. Only very recently have been used more explicit criteria in epidemiological studies
		There is no consistency regarding prevalence of allergy in CRS patients
	Similarity (analogy)	Both AR and CRS share the same trend of increasing prevalence
		Increased incidence of CRS in asthmatic patients

AFRS, allergic fungal rhinosinusitis; AR, allergic rhinitis; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; FESS, functional endoscopic sinus surgery; SCUAD, severe chronic upper airways disease.

a modifying role apart from its key role on type I hypersensitivity [31]. A possible explanation could be the IgE formation induced by superantigens. Superantigens seem to further modify the immune response and are responsible for activation of T and B cells, formation of local IgE in polyps, and could be causal agents in the intrinsic form of severe asthma [32].

Such superantigens include staphylococcal enterotoxins A and B.

In a Europe-wide epidemiological study, staphylococcal enterotoxin-IgE, even if undetectable in serum of CRSwNP patients [33], when present in polyps, was associated with asthma and especially severe, nonatopic late-onset asthma [34]. These mucosally formed IgE are polyclonic and functional, even in the absence of systemic IgE or positive skin-prick tests [35].

In a recent study, staphylococcal enterotoxin-IgE in combination with IL-5, ECP, and total IgE was significantly increased in recurrent polyps, illustrating a role of staphylococcal enterotoxins in recurrent disease [36].

Furthermore, serum staphylococcal enterotoxin-IgE antibodies, but not IgE against inhalant allergens, were identified as a risk factor for asthma severity, involving staphylococcal enterotoxins in the pathophysiology of severe asthma [37].

Table 2. Conclusions of studies in favor and against of allergy being a predisposing factor for chronic rhinosinusitis in adults

Studies in favor	Studies against
Adult literature	
Increased incidence of allergy in nasal polyp patients [5,6]	Possible selection or referral bias [10–13]
Increased percentage of nasal polyp in allergic patients [7]	No increased percentage of allergy in nasal polyp patients [6,14–18]
Immunotherapy increases success of surgery [8], especially in AFRS [9]	Presence of allergy does not affect symptom severity, surgery likelihood, and extent of disease on CT [19–21]

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

New studies

New studies have shown that amplification of T2 inflammation occurs via innate lymphoid cells (ILCs) [38▪]. These cells express surface receptors for epithelial-derived cytokines IL-25 and IL-33 [39]. These cytokines have been described lately and are released from damaged epithelial cells in response to allergens, viruses, and fungi [40▪]. After binding, significant secretion of IL-5 and IL-13 leads to inflammatory activation [41]. This can also happen with staphylococcal enterotoxins.

A recent study showed that IL-25/IL-33 receptors are also expressed in a group of Th2 cells, and after binding, marked release of IL-5/IL-13 induces more T2 inflammation [42▪▪].

Therefore, it seems that the classic way of activation of naïve T cells from antigen-presenting cell into a Th2 subtype and the proposed way of amplification by ILCs described before are both bypassed, thus suggesting that environmental triggers (viruses and allergens) may explain the intense inflammation in CRSwNP. This newly described mechanism could constitute a new field for developing biologics, targeting specific immune pathways especially for refractory cases.

A study published from Tomassen *et al.* [3▪▪], trying to identify inflammatory endotypes based on cluster analysis of biomarkers, confirmed that the presence of IL-5 remains the paramount factor dictating the phenotype with nasal polyps and asthma, and that the presence of staphylococcal enterotoxin-IgE remains associated with nasal polyps with intense eosinophilic inflammation with very high IgE concentrations and asthma comorbidity. However, there was evidence that IL-5 is not the only key to polyp formation for some groups. Interestingly, in a staphylococcal enterotoxin-IgE positive cluster, there was documented increased IL-22 production indicating Th22 involvement that was also observed to be induced by staphylococcal enterotoxins in patients with atopic dermatitis [43].

Finally, an IL-5 positive but eosinophil negative cluster with a polyp prevalence of around 50% had a Th17 neutrophil-type inflammation. Similar endotype has been documented in Chinese patients with nasal polyps. Of note, second-generation Asian patients with CRSwNP in the United States had a higher rate of noneosinophilic polyps than white patients as was recently shown [44▪].

Improving our treatment

Inasmuch as allergy and asthma are common in CRSwNP, we propose that screening tests should be considered as an option. Furthermore, we believe that targeted, symptom-specific therapy, and avoidance can potentially improve conditions mimicking CRS or ameliorate potential drivers of inflammation [4]. Wilson *et al.* [22] in his review for the role of allergy enhances our concept.

New therapies

Conventional treatment like corticosteroids when administered postoperatively can improve recurrence rates in cases of CRSwNP [45] but we are going through a new era of personalized medicine [46]. Even when treating with antibiotics, optimally we need inflammatory markers, inasmuch as patients with pronounced nasal polyp eosinophilia and elevated serum IgE are less likely to respond in comparison with neutrophilic nasal polyps. Endotyping patients and identifying specific cytokines and inflammatory cells allow us to use mAbs and other biologics to specifically block inflammatory pathways. IgE and ILs play a key role in allergy, asthma, and polyps' pathology and are potential targets. Of note, the price of this strategy in terms of both detecting these cytokines and the drug itself is a cardinal issue but identifying the exact group of patients and potential savings from fewer surgeries may establish their role mainly in refractory cases.

Omalizumab, already licensed for allergic asthma, is a humanized mAb (hmAb) that binds free IgE with high affinity and prevents its binding to IgE receptor on basophils, mast cells, and dendritic cells. Therefore, the allergic inflammation is reduced and improvement of symptoms is documented in asthma but also in AERD disease [47▪], although non-IgE-mediated. This may happen because many patients with AERD demonstrate elevated baseline IgE levels [48]. In a recent proof of concept study of allergic and nonallergic patients with CRSwNP and asthma, omalizumab significantly decreased the total nasal endoscopic score and improved nasal symptoms and sense of smell [49].

Patients with high serum IgE concentrations or unable to receive omalizumab could benefit from ligelizumab, a novel antibody with greater affinity for IgE than omalizumab. Studies are currently being performed in atopic patients [50], and its efficacy in nasal polyp and asthma remains to be evaluated.

Another fully hmAb, dupilumab, inhibits signaling of both IL-4 and IL-13, which have central role to Th2-mediated inflammation, by binding their common receptor. Dupilumab has demonstrated efficacy in patients with asthma and atopic dermatitis and also improved sinonasal symptoms in patients with asthma [51]. In a new randomized, double-blind, placebo-controlled study, dupilumab, when delivered subcutaneously, demonstrated

1068-9508 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

significant improvements in polyp size, SNOT-22 score, and smell among adults with nasal polyps refractory to intranasal corticosteroids. Moreover, the reduction of Th2 biomarkers, including IgE, which were elevated relatively to controls before the drug administration, further supports a common set of underlying Th2-inflammatory mechanisms in these diseases [52▪▪].

Mepolizumab, an anti-IL-5 hmAb, already used in eosinophilic conditions like asthma [53,54▪] prevents binding of IL-5 on the eosinophil receptor. A proof of concept study [55] confirmed significant reduction in polyp score and improvement in other clinical outcomes in patients with refractory polyposis after two single injections.

A new biologic factor has been developed (GATA-3 DNAzyme) that could possibly deactivate all Th2 cytokines through blockage of the transcription factor GATA-3 in Th2 and ILCs. Experimental studies demonstrated a significant reduction of the immediate and late allergic phases, as well as markers associated with Th2 reactions, including IL-5, showing high potential in the treatment of Th2-associated diseases, including nasal polyps but with the risk of side effects due to systemic applications and probably high costs [56▪].

Resorting to surgery

Regarding CRSwNPs with comorbid asthma, older studies have shown that there is improvement on asthma outcomes after treating CRSwNP, and new studies show that CRS patients with both asthma and polyps or asthma alone experience a larger quality of life improvement in SNOT-22 after functional endoscopic sinus surgery than CRS patients without asthma or nasal polyps [57].

Hopkins *et al.* [58▪] in a prospective study demonstrated that patients who had delayed surgery experienced less improvement in SNOT-22 scores than patients who operated earlier, and asthma and allergies were significantly more prevalent in the late versus the early and mid-cohorts indicating that we should not delay surgery too long. An explanation could be the early radical removal of the inflammatory load [59]. An interesting study that evaluates the impact of medically rCRS on the incidence of asthma provides evidence that ESS reduces the incidence of asthma postoperatively. This reduction was bigger in the groups operated earlier [30▪▪]. So it seems that early surgery averts the development of refractory disease. Additional validity on this clinical observation comes from a study [3▪▪] that shows that inflammatory profiles of asthmatic patients evolve over time within patients. Indeed, some patients coexpressed IL-17 apart from IL-5 over an average period of 5 years.

CONCLUSION

So far, a lot of studies have been published regarding the pathophysiology of CRSwNP but we have not fully elucidated the exact mechanism of polyp formation and how allergy and asthma affect the severity of disease. Although common inflammatory mechanisms seem to link these diseases, an explicit causal relationship cannot be established. The concept of endotyping polyps has paved the way on the direction of future research.

Our goal in CRS management is treating each patient individually, according to his inflammatory profile using data from basic research to the planning of a patient-centered, personalized therapy. Randomized multicenter trials are crucial in this effort; however, their limitations in guiding us to draw conclusions for individual patients must always be acknowledged if we want to aim for really personalized medicine.

To best help our patients, we need to be familiar with immunology and lower airway diseases and work closely with chest physicians and allergists – in airway diseases as in medicine in general, a multidisciplinary team approach is mandatory.

Acknowledgements

We would like to acknowledge Dr Hatzimanolis, Hygeia Hospital, for his support.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Soler ZM, Wittenberg E, Schlosser RJ, *et al.* Health state utility values in patients undergoing endoscopic sinus surgery. Laryngoscope 2011; 121:2672–2678.
2. Remenschneider AK, D'Amico L, Gray ST, *et al.* The EQ-5D: a new tool for studying clinical outcomes in chronic rhinosinusitis. Laryngoscope 2015; 125:7–15.
3. ▪▪ Tomassen P, Vandeplas G, Van Zele T, *et al.* Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol 2016; 37:1449–1456. e4. pii: S0091-6749(16)00184-6.

This study tries to identify inflammatory endotypes. The result was 10 clusters defined by the composition of inflammatory markers. Those endotypes correlate with the clinical expression of disease, polyps, and asthma.

4. Georgalas C, Vlastos I, Picavet V, *et al.* Is chronic rhinosinusitis related to allergic rhinitis in adults and children? Applying epidemiological guidelines for causation. Allergy 2014; 69:828–833.
5. Blumstein GI, Tuft L. Allergy treatment in recurrent nasal polyposis: its importance and value. Am J Med Sci 1957; 234:269–280.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

6. Drake-Lee AB. Histamine and its release from nasal polyps: preliminary communication. J R Soc Med 1984; 77:120–124.
7. Kern R. Allergy: a constant factor in the etiology of so-called mucous nasal polyps. J Allergy 1993; 4:483.
8. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Immunotherapy in patients undergoing functional endoscopic sinus surgery. Otolaryngol Head Neck Surg 1994; 110:406–412.
9. Bassichis BA, Marple BF, Mabry RL, *et al.* Use of immunotherapy in previously treated patients with allergic fungal sinusitis. Otolaryngol Head Neck Surg 2001; 125:487–490.
10. Hamilos DL, Leung DY, Wood R, *et al.* Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. J Allergy Clin Immunol 1995; 96:537–544.
11. Slavin RG. Sinusitis in adults and its relation to allergic rhinitis, asthma, and nasal polyps. J Allergy Clin Immunol 1988; 82:950–956.
12. Hamilos DL, Leung DY, Wood R, *et al.* Chronic hyperplastic sinusitis: association of tissue eosinophilia with mRNA expression of granulocyte-macrophage colony-stimulating factor and interleukin-3. J Allergy Clin Immunol 1993; 92:39–48.
13. Shapiro GG. Role of allergy in sinusitis. Pediatr Infect Dis 1985; 4:S55–S59.
14. Bunnag C, Pacharee P, Vipulakom P, Siriyananda C. A study of allergic factor in nasal polyp patients. Ann Allergy 1983; 50:126–132.
15. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy 1971; 29:631–634.
16. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6037 patients. J Allergy Clin Immunol 1977; 59:17–21.
17. Pepys J, Duveen GW. Negative skin tests in allergic rhinitis and nasal polyposis. Int Arch Allergy Appl Immunol 1951; 2:147–160.
18. Liu CM, Shun CT, Hsu MM. Lymphocyte subsets and antigen-specific IgE antibody in nasal polyps. Ann Allergy 1994; 72:19–24.
19. Keith PK, Conway M, Evans S, *et al.* Nasal polyps: effects of seasonal allergen exposure. J Allergy Clin Immunol 1994; 93:567–574.
20. Robinson S, Douglas R, Wormald PJ. The relationship between atopy and chronic rhinosinusitis. Am J Rhinol 2006; 20:625–628.
21. Pearlman AN, Chandra RK, Chang D, *et al.* Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. Am J Rhinol Allergy 2009; 23:145–148.
22. Wilson KF, McMains KC, Orlandi RR. The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. Int Forum Allergy Rhinol 2014; 4:93–103.
23. Bent JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1994; 111:580–588.
24. ■ Orlandi RR, Kingdom TT, Hwang PH, *et al.* International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol 2016; 6:S22–S209.
Consensus that creates EB reviews about chronic rhinosinusitis (CRS) and gives recommendations about management issues depending on level of evidence.
25. Krouse JH, Brown RW, Fineman SM, *et al.* Asthma and the unified airway. Otolaryngol Head Neck Surg 2007; 136:S75–S106.
26. Williamson PA, Vaidyanathan S, Clearie K, *et al.* Airway dysfunction in nasal polyposis: a spectrum of asthmatic disease? Clin Exp Allergy 2011; 41:1379–1385.
27. Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the severe asthma research program. Am J Respir Crit Care Med 2010; 181:315–323.
28. Lehrer E, Mullol J, Agredo F, Alobid I. Management of chronic rhinosinusitis in asthma patients: is there still a debate? Curr Allergy Asthma Rep 2014; 14:440.
29. Alobid I, Cardelus S, Benitez P, *et al.* Persistent asthma has an accumulative impact on the loss of smell in patients with nasal polyposis. Rhinology 2011; 49:519–524.
30. ■■ Benninger MS, Sindwani R, Holy CE, Hopkins C. Impact of medically recalcitrant chronic rhinosinusitis on incidence of asthma. Int Forum Allergy Rhinol 2016; 6:124–129.
Retrospective study that evaluates yearly incidence and prevalence of newly diagnosed asthmatics in groups of CRS patients depending on time of surgery. Secondary analysis shows that allergic rhinitis was a significant risk factor for asthma in these patients.
31. Bachert C, Zhang N. Chronic rhinosinusitis and asthma: novel understanding of the role of IgE 'above atopy'. J Intern Med 2012; 272:133–143.
32. Bachert C, Zhang N, Holtappels G, *et al.* Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with co-morbid asthma. J Allergy Clin Immunol 2010; 126:962–968.
33. Schiappoli M, Lombardo C, Bortolami O, *et al.* IgE to staphylococcal enterotoxins are undetectable in sera from patients with nasal polyposis. Eur Ann Allergy Clin Immunol 2012; 44:251–252.
34. Tomassen P, Jarvis D, Newson R, *et al. Staphylococcus aureus* enterotoxin-specific IgE is associated with asthma in the general population: a GA^{2}LEN study. Allergy 2013; 68:1289–1297.
35. Matsuwaki Y, Uno K, Okushi T, *et al.* Total and antigen- (fungi, mites and staphylococcal enterotoxins) specific IgEs in nasal polyps is related to local eosinophilic inflammation. Int Arch Allergy Immunol 2013; 161 (Suppl 2): 147–153.
36. Van Zele T, Holtappels G, Gevaert P, Bachert C. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy 2014; 28:192–198.
37. Bachert C, van Steen K, Zhang N, *et al.* Specific IgE against *Staphylococcus aureus* enterotoxins: an independent risk factor for asthma. J Allergy Clin Immunol 2012; 130:376–381.e8.
38. ■ Vreugde S, Wormald PJ. Innate lymphoid type 2 cells in chronic rhinosinusitis. Curr Opin Allergy Clin Immunol 2016; 16:7–12.
Recent review that describes the role of innate lymphoid cell (ILC) type 2 in innate and adaptive immunity cell with a critical role for ILC2 not only in mounting type 2 immune responses at barrier surfaces, but also in tissue-repair responses and normal homeostatic functions. It gives important insights in particular in the context of allergic inflammatory diseases, emphasizing a critical role for ILC2 in diseases of the upper and lower airways such as allergy, asthma, and CRS.
39. Mjösberg JM, Trifari S, Crellin NK, *et al.* Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol 2011; 12:1055–1062.
40. ■ Martinez-Gonzalez I, Steer CA, Takei F. Lung ILC2s link innate and adaptive responses in allergic inflammation. Trends Immunol 2015; 36:189–195.
Shows that ILC2-derived cytokines are responsible not only for the innate responses underlying allergic inflammation but also for the initiation of the adaptive Th2 response.
41. Barlow JL, Peel S, Fox J, *et al.* IL-33 is more potent than IL-25 in provoking IL-13- producing nuocytes (type 2 innate lymphoid cells) and airway contraction. J Allergy Clin Immunol 2013; 132:933–941.
42. ■■ Lam EP, Kariyawasam HH, Rana BM, *et al.* IL-25/IL-33-responsive TH2 cells characterize nasal polyps with a default TH17 signature in nasal mucosa. J Allergy Clin Immunol 2016; 137:1514–1524.
Very interesting study that shows that a group of polyp-derived TH2 cells coexpressed IL-25 and IL-33 receptor and responded to IL-25 and IL-33 with enhanced IL-5 and IL-13 product.
43. Niebuhr M, Mainardy J, Heratizadeh A, *et al.* Staphylococcal exotoxins induce interleukin 22 in human th22 cells. Int Arch Allergy Immunol 2014; 165:35–39.
44. ■ Mahdavinia M, Suh LA, Carter RG, *et al.* Increased noneosinophilic nasal polyps in chronic rhinosinusitis in US second-generation Asians suggest genetic regulation of eosinophilia. J Allergy Clin Immunol 2015; 135:576–579.
This study suggests that the inflammatory profile of polyps regarding eosinophilia may be genetically regulated inasmuch as in specific population expressed increased noneosinophilic nasal polyps.
45. Pundir V, Pundir J, Lancaster G, *et al.* Role of corticosteroids in functional endoscopic sinus surgery – a systematic review and meta-analysis. Rhinology 2016; 54:3–19.
46. Muraro A, Fokkens WJ, Pietikainen S, *et al.* European symposium on precision medicine in allergy and airways diseases: report of the European Union Parliament Symposium (October 14, 2015). Allergy 2016; 71:583–587.
47. ■ Bergmann KC, Zuberbier T, Church MK. Omalizumab in the treatment of aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract 2015; 3:459–460.
Interestingly, this study shows that despite the fact that IgE does not feature prominently in aspirin-exacerbated respiratory disease (AERD) pathogenesis, AERD patients seem to benefit from omalizumab.
48. Johns CB, Laidlaw TM. Elevated total serum IgE in nonatopic patients with aspirin-exacerbated respiratory disease. Am J Rhinol Allergy 2014; 28:287–289.
49. Gevaert P, Calus L, Van Zele T, *et al.* Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013; 131:110–116.e1.
50. Arm JP, Bottoli I, Skerjanec A, *et al.* Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy 2014; 44:1371–1385.
51. Wenzel S, Ford L, Pearlman D, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 2013; 368:2455–2466.
52. ■■ Bachert C, Mannent L, Naclerio RM, *et al.* Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 2016; 315:469–479.
A randomized, placebo-controlled clinical trial that showed that dupilumab improved polyp score, Lund–Mackay score, SNOT, and sense of smell among the 60 patients, 35 of them with comorbid asthma.
53. Robinson DS, Kariyawasam HH. Mepolizumab for eosinophilic severe asthma: recent studies. Expert Opin Biol Ther 2015; 15:909–914.
54. ■ Menzella F, Lusuardi M, Galeone C, *et al.* Profile of anti-IL-5 mAb mepolizumab in the treatment of severe refractory asthma and hypereosinophilic diseases. J Asthma Allergy 2015; 8:105–114.
The introduction of mepolizumab, a fully humanized mAb that binds to IL-5, may represent a useful therapeutic option to control exacerbations and improve asthma-related quality of life in a subgroup of patients with persistent airway eosinophilia and moderate-to-severe asthma and other hypereosinophilic disorders like sinonasal polyposis and allergic rhinitis.

1068-9508 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

55. Gevaert P, Van Bruaene N, Cattaert T, *et al.* Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol 2011; 128:989–995.

56. Krug N, Hohlfeld JM, Kirsten AM, *et al.* Allergen-induced asthmatic responses ■ modified by a GATA-3 specific DNAzyme. N Engl J Med 2015; 372:1987–1995.
This study illustrates a potential target of Th2 inflammation, transcription factor GATA-3, and a new biologic factor (GATA-3 DNAzyme) that could possibly deactivate all Th2 cytokines through blockage of the transcription factor GATA-3 in Th2 and ILCs.

57. Zhang Z, Adappa ND, Doghramji LJ, *et al.* Quality of life improvement from sinus surgery in chronic rhinosinusitis patients with asthma and nasal polyps. Int Forum Allergy Rhinol 2014; 4:885–892.

58. Hopkins C, Rimmer J, Lund VJ. Does time to endoscopic sinus surgery impact ■ outcomes in chronic rhinosinusitis? Prospective findings from the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis. Rhinology 2015; 53:10–17.
Analysis of comorbidities such as asthma and allergy and preoperative computed tomography scores for patients that grouped based on time to surgery in three cohorts. Results show that patients with asthma and/or allergies are more likely to experience delayed surgical intervention versus other patients, and delaying surgical intervention may worsen long-term clinical outcomes.

59. Bassiouni A, Naidoo Y, Wormald PJ. When FESS fails: the inflammatory load hypothesis in refractory chronic rhinosinusitis. Laryngoscope 2012; 122: 460–466.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.