

Accepted Manuscript

Rethinking Chronic Rhinosinusitis Phenotypes

Larry Borish, MD

PII: S0091-6749(16)30954-X

DOI: [10.1016/j.jaci.2016.08.013](https://doi.org/10.1016/j.jaci.2016.08.013)

Reference: YMAI 12331

To appear in: *Journal of Allergy and Clinical Immunology*

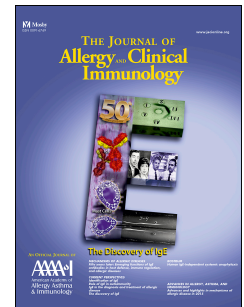
Received Date: 7 July 2016

Revised Date: 28 July 2016

Accepted Date: 8 August 2016

Please cite this article as: Borish L, Rethinking Chronic Rhinosinusitis Phenotypes, *Journal of Allergy and Clinical Immunology* (2016), doi: 10.1016/j.jaci.2016.08.013.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Rethinking Chronic Rhinosinusitis Phenotypes

Larry Borish, MD

Asthma and Allergic Disease Center

Carter Immunology Center

Departments of Medicine and Microbiology

University of Virginia Health System

Charlottesville, VA 22908

*to whom correspondence should be sent at: Asthma and Allergic Disease Center, Box 801355,
University of Virginia Health System, Charlottesville, VA 22908-1355; phone #: (434) 243-
6570, fax # (434) 924-5779, email: lb4m@virginia.edu

Supported by NIH: RO1 AI1057438, UO1 AI100799, R56 AI120055, and UO1AI123337

Running Title: Rethinking CRS Phenotypes

The author reports no relevant conflict of interest

It is the currently accepted practice to sort chronic rhinosinusitis (CRS) into two phenotypes distinguished solely according to the presence (CRSw) or absence (CRSs) of nasal polyps (NPs). This dichotomy was based in part on the relative ease of determining whether nasal polyps are present and the seeming distinct immune and pathological presentations of these two conditions (1). Thus, the presence of NPs suggests the presence of an eosinophilic disease with a prominent Th2 cytokine signature and, in particular, the presence of the most important cytokine driving eosinophilic inflammation, interleukin (IL)-5. In contrast, defining the immune and pathological basis underlying CRSs/NPs has been more controversial but is less likely to be characterized by eosinophils and a Th2/IL-5 signature (2).

But this concept that the presence of NPs alone could be the basis for assuming the presence of an IL-5^{high} eosinophilic process has been rife with controversy. This controversy included the striking observation that whereas NPs in European studies seemingly were universally eosinophilic in nature, those evaluated in China were equally universally neutrophilic. And, for those of us practicing elsewhere, the extent of eosinophilia can be quite variable. For example, at the University of Virginia, pathological examination of 76 consecutive surgically-derived polyps demonstrates a split of 84.2%-15.8% between those that are predominantly eosinophilic and neutrophilic, respectively (unpublished). The study by Bachert et al. in the current issue of *J Allergy and Clin. Immunol.* (3) is therefore a valuable advance in our understanding of these regional difference in CRS pathology and immune profiles and more importantly begins to force a rethinking of how CRS should be subgrouped.

The timing for this rethinking is especially appropriate, as although in 2016 there are still no FDA approved therapeutics for CRS, we are on the cusp of major pharmacologic advances.

However, the specific mechanistic-based targeting of CRS therapeutics will require demonstrating the presence of an appropriate histological and immune signature that will predict efficacy. For example, just as in asthma where there was from the beginning a compelling literature that corticosteroid (CCS) efficacy is dependent on the presence of eosinophils, this will almost certainly also be true in CRS where highly variable responsiveness to CCS is also observed (4). And, similarly, preliminary studies evaluating the benefit of anti-IL-5 in CRS have shown that – as with asthma – the presence of an eosinophil^{high}/IL-5^{high} state is required to predict responsiveness (5).

The problem is that while in Europe, Australia, the US, and Japan, CRSwNPs is most often an IL-5^{high} state, large numbers of these polyps display neither IL-5 (17% in Benelux in the current study) nor a high EPO/MPO ratio (~30% in Benelux). These individuals will be unlikely to respond to IL-5 antagonism or, perhaps, to steroid irrigation or other Th2 antagonists. And, obviously, the response rate with these agents in Chengzu, China will be even lower. But what is also intriguing is that many of the subjects in the current study *without* NPs displayed a Th2 high signature with elevated levels of IL-5 (30% in Benelux) along with high concentrations of ECP (~40%). The absence of polyps in these patients reflects either the location of the inflammation in the sinus (away from any sinus ostia) or merely that the NPs have not developed – yet. Either way, these are presumably patients who will respond to therapies targeting these immune processes and, more importantly, this suggests that they have an endotype *identical* to those with Th2^{high}/IL-5^{high}/eosinophil^{high} CRSwNPs.

While early studies argued that CRSsNPs seemed to be a Th1 or perhaps even a Th17 prominent disease (1) more recent studies have not been able to confirm this and,

alternatively, suggest that this condition is most often not associated with any particular T effector signature (6). The current study confirms that a plurality of these subjects do not demonstrate cytokines associated with any T effector signature. What is again interesting, is that the pattern of inflammation and cytokines observed in CRSsNPs is quite similar to that observed in patients with *non-eosinophilic* CRSwNP disease. This, again, suggests that the IL-5^{low}/eosinophil^{low} signature represents a distinct endotype (or, perhaps, distinct endotypes) which may be present in most CRSsNPs samples and – outside of China – a significant minority of CRSwNP samples. A compelling argument can therefore be made that it is time to move past the subgrouping of CRS solely on the basis of whether or not polyps exist but instead demand that pathology be obtained from patients with CRS – especially those undergoing surgery – to permit initiation of appropriate endotype-specific treatments.

Another question arising from this paper is what is driving these distinct presentations of CRS. Presumably there are genetic and environmental factors involved. However, what is particularly intriguing is that these presentations are not fixed but are evolving over time (7, 8). It has been argued that there have been distinct “allergy” epidemics: those for allergic rhinitis (1870-1920), asthma (1960-1990), and food allergy (1990-present), and perhaps a fourth epidemic if we include eosinophilic esophagitis (EoE) (9). EoE seemingly did not exist or at least barely registered just a generation ago. It seems plausible that, just as eosinophils did not used to attack the esophagus, perhaps until recently they seldom attacked the sinuses. CRS itself is less frequent in China with a prevalence of 2.1-8% compared to the 7-27% prevalence reported in Europe (10). Perhaps the seemingly unique presentation of non-eosinophilic CRS in China represents the historic frequency of neutrophilic/IL-5^{low} CRS in all human populations. The

actual prevalence of this particular phenotype may be similar in China and Belgium and, indeed, may be comparatively low. And, if true, like Thailand and Korea (7, 8), China will soon see an epidemic of eosinophilic CRS, which will become the most prominent presentation observed there as well.

In summary, this study makes several important advances in our understanding of CRS. CRS can present as at least two distinct diseases that can be defined histologically and immunologically by the presence or absence of an eosinophil^{high}/IL-5^{high} state. Currently, there are striking regional differences in the prevalence of these two phenotypes. In combination with studies showing the temporal evolution of non-eosinophilic into eosinophil predominant diseases, an intriguing implication is that eosinophilic CRS is a new disease created by a modern “hygiene”-associated life style and the sinuses can now join the ranks of the nose (AR), lung (asthma), and gut (EoE) as organs now routinely afflicted with a Th2/eosinophilic disease. This study also demonstrates that – although at varying frequencies – an eosinophil^{low}/IL-5^{low} process can be present in both CRSs and CRSwNP subjects and similarly, eosinophil^{high}/IL-5^{high} tissue samples can be identified in both of these traditional presentations. These endotypes will define individualized therapeutics, including predicting efficacy to anti-IL-5, other eosinophil antagonists, and likely CCS. The current study thus begins to make a compelling argument that it may be time to move past the defining of CRS purely on the basis of whether or not there are nasal polyps and instead require pathological (and perhaps immunological) analysis of tissue samples as the proper basis for subgrouping/endotyping.

Bibliography

1. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, Schleimer RP, Ledford D. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2013; 131: 1479-1490.
2. Mahdavinia M, Suh LA, Carter RG, Stevens WW, Norton JE, Kato A, Tan BK, Kern RC, Conley DB, Chandra R, Lavin J, Peters AT, Grammer LC, 3rd, Schleimer RP. 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.
3. Wang X, Zhang N, Bo M, Holtappels G, Zheng M, Lou H, Wang H, Zhang L, Bachert C. Diversity of T-helper cytokine-profiles in chronic rhinosinusitis: A multicenter study in Europe, Asia and Oceania. *Journal of Allergy and Clinical Immunology* 2016; (in press).
4. Steinke JW, Payne SC, Tessier ME, Borish LO, Han JK, Borish LC. Pilot study of budesonide inhalant suspension irrigations for chronic eosinophilic sinusitis. *J Allergy Clin Immunol* 2009; 124: 1352-1354 e1357.
5. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, Holtappels G, Tavernier J, van Cauwenberge P, Bachert C. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol* 2006; 118: 1133-1141.
6. Stevens WW, Ocampo CJ, Berdnikovs S, Sakashita M, Mahdavinia M, Suh L, Takabayashi T, Norton JE, Hulse KE, Conley DB, Chandra RK, Tan BK, Peters AT, Grammer LC, 3rd,

- Kato A, Harris KE, Carter RG, Fujieda S, Kern RC, Schleimer RP. Cytokines in Chronic Rhinosinusitis. Role in Eosinophilia and Aspirin-exacerbated Respiratory Disease. *Am J Respir Crit Care Med* 2015; 192: 682-694.
7. Katotomichelakis M, Tantilipikorn P, Holtappels G, De Ruyck N, Feng L, Van Zele T, Muangsomboon S, Jareonchasri P, Bunnag C, Danielides V, Cuvelier CA, Hellings PW, Bachert C, Zhang N. Inflammatory patterns in upper airway disease in the same geographical area may change over time. *American journal of rhinology & allergy* 2013; 27: 354-360.
8. Kim SJ, Lee KH, Kim SW, Cho JS, Park YK, Shin SY. Changes in histological features of nasal polyps in a Korean population over a 17-year period. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* 2013; 149: 431-437.
9. Platts-Mills TA. The allergy epidemics: 1870-2010. *J Allergy Clin Immunol* 2015; 136: 3-13.
10. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang de Y, Wormald PJ. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012: 3 p preceding table of contents, 1-298.