

Chronic rhinosinusitis endotyping: Sharpening the focus on inflammation



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The heterogeneity of allergic diseases, such as asthma, has been pondered since the 1940s-1950s. The late Dr Richard Farr described the heterogeneity of asthma in terms of a 3-dimensional structure akin to a Rubik's Cube, with each of the small components of the cube representing a different phenotype. He and his longtime colleague, Dr Sheldon L. Spector, wrote about the heterogeneity of asthma as far back as 1976.¹ It was believed by Drs Spector and Farr that each of the different asthma phenotypes would have a different underlying pathophysiologic basis, even though the components of this were far from clear at the time. Over the ensuing years, much has been learned to validate their belief.

The term endotype was proposed by Lotvall et al² in 2011 to describe the link between the underlying pathophysiologic mechanism or mechanisms and subtypes of asthma and, by extrapolation, other diseases. There is nothing unique about asthma or allergic disease in this regard, but the term endotype has been applied mainly to studies of allergic and respiratory diseases, including chronic rhinosinusitis (CRS).^{3,4} The conceptual framework of endotyping dovetails with interest in personalized medicine and has its analogy in other fields based on a similar conceptual framework, such as molecular oncology, which is based on characterizing tumors based on mutation status of key oncogenes and growth factors. In each instance the hope is that endotyping will facilitate the design of more targeted and appropriate treatments for disease.

There is an ever-growing array of technologies that has expanded our capacity to endotype diseases far beyond traditional pathologic methods, including gene expression profiling; measurement of cytokines, profibrotic factors, and other key regulatory or signaling molecules at the level of translated proteins; and measurement of mediators or metabolic products in tissues or exhaled air and metabolomics. In addition, related technologies, such as delineation of tissue microbiomes and broad-based platforms that examine genetic polymorphisms, gene mutations, and abnormalities of gene copy number, can all be applied to endotyping.

In this issue of the *Journal*, Tomassen et al⁵ present their work to define “inflammatory endotypes” of CRS. The analytic foundation of this study is principal component analysis, an advanced statistical technique. Ultimately, the authors defined a group of 10 CRS inflammatory endotype “clusters” and used a number of validation steps to confirm the optimal number of CRS clusters. The endotypes identified showed a good general agreement with the established clinical classification of CRS into the phenotypes of chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP).⁶ Four clusters were identified with low or undetectable IL-5, eosinophil cationic protein, IgE, and albumin concentrations. Three of these 4 IL-5-negative clusters had either no inflammation or a T_H22 or T_H1 profile and clinically resembled a predominant CRSsNP phenotype without an increased prevalence of asthma. One cluster had a T_H17 profile and was comprised of a mixed group of patients with CRSsNP and patients with CRSwNP. Conversely, 6 clusters were identified with high concentrations of IL-5, eosinophil cationic protein, IgE, and albumin. The IL-5⁺ clusters were further divided into a group of 3 clusters with moderate IL-5 concentrations, which turned out to be comprised of a mixed group of patients with CRSsNP and patients with CRSwNP with an increased prevalence of asthma and a cluster with high IL-5 levels comprised almost exclusively of patients with nasal polyps, the majority of whom (71%) also had asthma. In the 2 IL-5-high clusters demonstrating the highest concentrations of IgE and asthma prevalence, tissues from all of the patients also expressed *Staphylococcus aureus*-specific IgE. Thus 10 distinct clusters were identified in this analysis, and these clusters showed moderately strong relationships with the known clinical phenotypes of CRSsNP and CRSwNP but were claimed by the authors to further differentiate them, providing “a more accurate description of the inflammatory mechanisms involved than phenotype information only.” This point could be challenged because no compelling evidence was presented as to what additional insight was gained by the analysis.

Curiously, the proportion of patients reporting aspirin sensitivity was not significantly different across clusters, which is in contradiction with other studies.⁷ Relying on patient self-report of aspirin sensitivity might have contributed to this apparently contradictory finding.

A limitation of the study by Tomassen et al⁵ is that it did not include other clinical phenotypes of CRS, such as allergic fungal rhinosinusitis or cystic fibrosis, both of which are typically associated with nasal polyposis. It could have been challenging to include such patients, considering that patients with allergic fungal rhinosinusitis and those with cystic fibrosis comprise only a small percentage of cases of CRS. The study by Tomassen et al⁵ therefore serves mainly as a validation of previously

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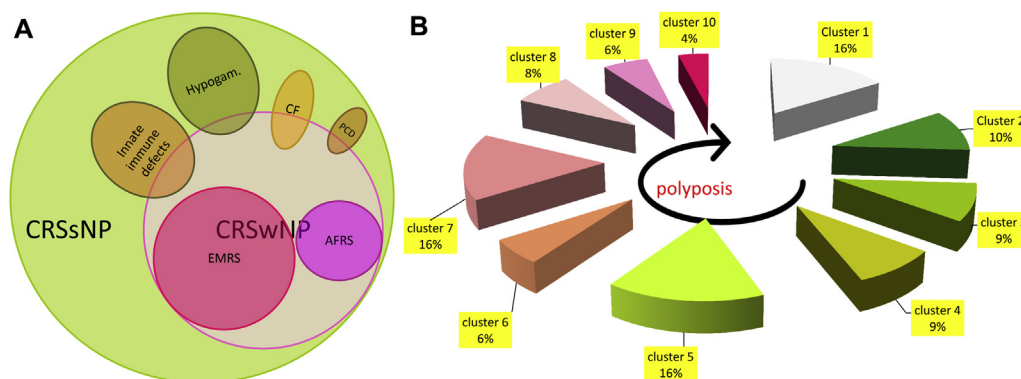


FIG 1. Classification of CRS based on clinical subsets (A) and endotypes (B). Fig 1, A, Venn diagram depicting the clinical subsets of CRS. All CRS is either classified as CRSsNP or CRSwNP. Allergic fungal rhinosinusitis (AFRS) is considered a subset of CRSwNP.⁶ Eosinophilic mucin rhinosinusitis (EMRS) is a subset of CRSwNP characterized by the presence of eosinophilic mucin without fungal hyphae.¹² Eosinophilic mucin rhinosinusitis has been reported to be more common than AFRS.¹³ Subsets of patients with CRS with an underlying problem, such as an innate immune defect, hypogammaglobulinemia (Hypogam.), cystic fibrosis (CF), or primary ciliary dyskinesia (PCD),¹⁴ are depicted as overlapping subsets of CRSsNP and CRSwNP, although the proportion of cases within the CRSsNP and CRSwNP groups is variably reported and not intended to be precisely depicted in the figure. Fig 1, B, Endotypes of CRS based on the study of Tomassen et al⁵ show some overlap between the CRSsNP and CRSwNP subsets, with the highest prevalence of polyposis in clusters 8, 9, and 10. Clusters 1-4 have low or undetectable IL-5 and clinically resemble a predominant CRSsNP phenotype. Clusters 5-10 have elevated IL-5 levels and show a progression toward a higher prevalence of CRSwNP and asthma.

described inflammatory markers for CRSsNP and CRSwNP, with the endotypic markers studied being confined to those already used to differentiate these conditions.

Fig 1 contrasts our current understanding of the clinical subsets of CRS with new insights gleaned from this study regarding CRS inflammatory endotypes.

A further limitation is that the study also did not include other inflammatory markers implicated in the pathogenesis of CRSwNP and under serious consideration as potential “druggable” targets, such as IL-13⁸ and the epithelial cytokines thymic stromal lymphopoietin⁹ and IL-33.¹⁰ Inclusion of these could have helped to further differentiate the clusters of CRS and offer additional insight into potential therapeutic targets.

Another important consideration in principal component analysis is that of confounding effects, such as cigarette smoke or other environmental exposures, disease state (eg, chronic vs chronic with disease exacerbation), medication use, comorbid conditions, or superimposed acute sinus infection.¹¹ In the study by Tomassen et al,⁵ the effect of cigarette smoke exposure on CRS endotypes might have been underappreciated because the magnitude of cigarette smoke exposure was not quantified, and the prevalence of smoke exposure in this study was significantly higher (current smokers: 29% of cases and 26% of control subjects; ever smokers: 65% of cases and 47% of control subjects) than in other parts of the world, such as the United States.

Finally, the “eyeball” test of the 10 CRS clusters illustrated in Fig 3 of the Tomassen et al⁵ article suggests at least that there is a continuum of inflammatory markers giving rise to significant overlap of the identified clusters. This is especially noticeable in clusters 5 through 7 and clusters 8 through 10. The question is whether there is true biologic meaning to each of the clusters within these groups or whether the subtle differences between the clusters are due to confounding variables, such as sampling variability, medication effects, or overlying infection.

In summary, the article by Tomassen et al⁵ serves mainly as a validation of previously published studies delineating pathologic differences between patients with CRSsNP and those with CRSwNP but represents an important step forward in more precisely parsing out the endotypes of CRS. The novelty of the findings is limited because of the somewhat restricted focus of the investigation on previously established pathologic correlates of disease while not including other potentially important pathologic factors. Ultimately, the validity of the analysis depends on how exhaustively the principal variables were selected for the analysis, how well the clinical spectrum of CRS was characterized in the patient population, how representative the samples were of the underlying disease, how robustly the measurements were performed, and how well confounding effects were minimized. The information derived from this type of study should stimulate additional hypothesis testing and provide additional rationale for design of novel therapeutic agents (eg, use of targeted anticytokine biologics or small-molecule inhibitors) for the treatment of CRS.

On the 40th anniversary of their article,¹ I would like to acknowledge the recent passing of Dr Spector who, along with Dr Farr, was an inspiration to me in my early career at National Jewish in Denver, Colorado.

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