Check for updates

REVIEW

Recent advances in understanding chronic rhinosinusitis endotypes [version 1; peer review: 2 approved]

Eric F. Succar, Justin H. Turner

Department of Otolaryngology-Head and Neck Surgery, Vanderbilt University Medical Center, Nashville, TN, 37232, USA

V1 First published: 07 Dec 2018, 7(F1000 Faculty Rev):1909
<https://doi.org/10.12688/f1000research.16222.1>

Latest published: 07 Dec 2018, 7(F1000 Faculty Rev):1909
<https://doi.org/10.12688/f1000research.16222.1>

Abstract

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disease with an as-yet-undefined etiology. The management of CRS has historically been phenotypically driven, and the presence or absence of nasal polyps has frequently guided diagnosis, prognosis, and treatment algorithms. Research over the last decade has begun to question the role of this distinction in disease management, and renewed attention has been placed on molecular and cellular endotyping and a more personalized approach to care. Current research exploring immunologic mechanisms, inflammatory endotypes, and molecular biomarkers has the potential to more effectively delineate distinct and clinically relevant subgroups of CRS. The focus of this review will be to discuss and summarize the endotypic characterization of CRS and the potential diagnostic and therapeutic implications of this approach to disease management.

Keywords

cytokine, T-helper cell, phenotype, nasal polyps, endotype, cluster

Open Peer Review

Approval Status

	1	2
version 1 07 Dec 2018

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Murugappan Ramanathan Jr**, Johns Hopkins University School of Medicine, Baltimore, USA
2. **Zheng Liu**, Huazhong University of Science and Technology, Wuhan, China

Any comments on the article can be found at the end of the article.

Corresponding author: Justin H. Turner (justin.h.turner@vanderbilt.edu)

Author roles: Succar EF: Conceptualization, Methodology, Writing – Original Draft Preparation; Turner JH: Conceptualization, Funding Acquisition, Investigation, Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: JHT has received grant support from the National Institutes of Health (NIH)/National Institute of Deafness and Communication Disorders and additional support from the NIH/National Institute of Allergy and Infectious Diseases. He receives salary and other support through NIH RO3 DC014809, L30 AI113795, and CTSA award UL1TR000445 from the National Center for Advancing Translational Sciences (NCATS). The manuscript contents are solely the responsibility of the authors and do not necessarily represent official views of the NCATS or the NIH.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2018 Succar EF and Turner JH. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Succar EF and Turner JH. **Recent advances in understanding chronic rhinosinusitis endotypes [version 1; peer review: 2 approved]** F1000Research 2018, 7(F1000 Faculty Rev):1909 <https://doi.org/10.12688/f1000research.16222.1>

First published: 07 Dec 2018, 7(F1000 Faculty Rev):1909 <https://doi.org/10.12688/f1000research.16222.1>

Background

Chronic rhinosinusitis (CRS) affects more than 4% of the US population and results in substantial economic burden to the health-care system^{1–4}. The medical and surgical management of CRS has changed incrementally over the last two decades; however, the recent introduction of humanized monoclonal antibodies that target individual inflammatory mediators has the potential to change the course of treatment for millions of patients. Treatment success will likely depend on appropriate patient selection and improved understanding of CRS pathophysiology. Recent research has begun to explore the heterogeneity of CRS by using unbiased approaches that incorporate clinical, demographic, and inflammatory variables. These analyses have moved beyond simple phenotypic classifications of CRS and instead have set out to differentiate CRS on the basis of cytokines and other inflammatory mediators that may be more relevant to disease mechanisms. The identification of multiple putative inflammatory endotypes, with relative consistency between studies, suggests that this may be a valid approach for characterizing CRS inflammation, predicting treatment outcomes, and identifying patients who may benefit from targeted therapeutics. This review will summarize recent advances in the identification and characterization of CRS endotypes and review potential impacts on patient care.

Chronic rhinosinusitis pathophysiology

Unfortunately, research into CRS disease mechanisms has been limited by a lack of validated animal models and the complexity of the disease itself. Although the pathophysiology of CRS is incompletely defined, current evidence suggests that both host (altered innate and adaptive immunity and genetics) and environmental (microbial pathogens and allergic sensitivity) factors likely play a cooperative role in disease initiation and progression^{5–8}. CRS is largely a mucosal disease with locoregional inflammation in the paranasal sinuses and upper airway that does not typically extend to the systemic circulation. This conclusion is supported by studies that show a lack of specific correlation between peripheral inflammatory markers and CRS subtypes^{9–11}. Patients with CRS frequently have altered mucosal innate immune responses and a propensity toward infection or colonization (or both) by microbial pathogens^{12,13}. This may derive from epithelial barrier dysfunction, a common finding in CRS that potentially results in compromised host defense and reduced tolerance to common microbial antigens^{14–16}. Epithelium-derived cytokines and chemokines subsequently can drive T cell-, B cell-, and innate lymphoid cell-mediated immune responses^{17–20}. T helper cell responses in CRS are highly variable, and a combination of Th1, Th2, Th17, and likely other T helper subsets drives the production of specific cytokines and results in a persistent inflammatory state^{21–23}. Furthermore, CRSwNP is frequently associated with infiltration by plasma cells and increased local production of immunoglobulin E (IgE) antibodies^{24–26}. Differential tissue infiltration by eosinophils or neutrophils (or both) is typical in CRS and governed by T cell-mediated immune responses and the resulting cytokine milieu.

The role of eosinophilic/Th2 inflammation in the pathophysiology of CRSwNP has been the focus of significant research.

Currently, monoclonal antibodies that are being investigated for use in CRS target eosinophilic/Th2 pathways²⁷. Neutrophils have been shown to drive inflammation in subsets of steroid-resistant CRSwNP and CRSsNP^{28,29}. Understanding how neutrophils impact mucosal barriers, tissue remodeling, and polyp formation and delineating immune factors that drive the process have potential diagnostic and therapeutic implications. Recent studies suggest that interleukin-1 beta (IL-1 β), IL-6, IL-8, oncostatin M, transforming growth factor-beta, and IL-36 γ play a role in the pathophysiology of neutrophilic inflammation in CRS^{28,29}. A greater understanding of these pathways may guide future investigation into the use of monoclonal antibodies targeting neutrophilic pathways in CRS.

Chronic rhinosinusitis phenotypes

Clinical phenotypes use a combination of observable features to differentiate patients with the same diagnosis. CRS phenotyping most commonly differentiates patients on the basis of the presence or absence of nasal polyps, as this is an easily identifiable trait that can be recognized in clinical practice. However, additional phenotypes—including CRS associated with aspirin-exacerbated respiratory disease, allergic fungal rhinosinusitis, and cystic fibrosis-associated CRS—have been described and are commonly used clinically. Although these phenotypes help to distinguish patients on the basis of disease behavior and have an underlying biological basis, they generally do not adequately explain underlying disease pathophysiology. For example, CRS phenotypes have typically been associated with characteristic immune signatures, with CRSsNP typically being linked with elevation of Th1-associated cytokines and CRSwNP being associated with a Th2 or mixed Th1/Th2 response^{30,31}. However, this rigid dichotomy is being questioned, and it is now commonly accepted that both CRSsNP and CRSwNP can present with a combination of Th1-, Th2-, and Th17-associated signatures^{21,32–34}. There is also substantial geographic variability to underlying inflammatory burden that cannot be explained by differences in phenotype alone²³.

Chronic rhinosinusitis endotypes

It is clear that phenotypic classification of CRS does not adequately describe the complexity of the disorder⁵ and that multiple unique inflammatory subtypes or endotypes likely exist within each phenotype³⁵. Not surprisingly, outcomes guided by phenotypic classification are often difficult to predict³⁶. The identification of inflammatory CRS endotypes has the potential to guide treatment and offer alternatives to patients who are refractory to traditional medical and surgical therapies³⁷. This approach has been used successfully in a number of inflammatory diseases, including eosinophilic esophagitis and asthma^{38–42}. As summarized previously, targeted characterization of inflammatory markers has identified Th1-, Th2-, and Th17-driven inflammatory signatures in subsets of patients with CRS. In contrast, more recent studies have used unstructured approaches that incorporate multi-dimensional data to identify clusters of patients with presumably similar mechanisms of disease^{32,33,43,44}. Whereas the number of identified clusters has varied between studies, the underlying characteristics of the clusters have resulted in generally consistent findings (Table 1). In a multi-institutional

Table 1. Summary of recent studies identifying chronic rhinosinusitis endotypes.

Authors	Year	Material analyzed	Sample size	Biomarkers	Clusters/endotypes
Tomassen <i>et al.</i> ³²	2016	Tissue (sinus mucosa/polyps)	173 patients with CRS, 89 controls	14	10
Divekar <i>et al.</i> ⁴³	2017	Tissue (ethmoid)	26 patients with CRS, 6 controls	41	3
Liao <i>et al.</i> ⁴⁴	2018	Tissue (ethmoid/polyp)	246 patients with CRS, 16 controls	39	7
Turner <i>et al.</i> ³³	2018	Mucus	90 patients with CRS, 17 controls	18	6

CRS, chronic rhinosinusitis.

European study, Tomassen *et al.* used hierarchical cluster analysis to analyze 14 inflammatory mediators in surgically obtained tissue from 173 patients with CRS and identified 10 distinct CRS clusters³². Clustering was driven primarily by (1) eosinophilic and Th2-related markers (IL-5 and IgE), (2) neutrophilic or pro-inflammatory mediators or both (IL-1 β , IL-6, IL-8, and myeloperoxidase), (3) Th17/Th22 markers (IL-17A, IL-22, and tumor necrosis factor- α), and (4) the Th1 cytokine interferon- γ (IFN- γ). About 60% of patients had a Th2-high signature with a high prevalence of nasal polyposis and asthma. In a similar approach, Liao *et al.* analyzed 246 Chinese patients with CRS and incorporated both inflammatory biomarkers and clinical/demographic variables in the clustering model⁴⁴. Seven distinct clusters were identified; however, in their study, in contrast to the study by Tomassen *et al.*, fewer than 20% of patients carried a dominant Th2 signature. The remaining clusters were characterized primarily by either mild inflammatory burden or neutrophilic inflammation. The authors also incorporated treatment outcomes into their analysis by comparing the frequency of “difficult-to-treat” CRS in each cluster. The Th2-dominant cluster was associated with severe clinical disease and poor treatment outcomes. However, a comparably larger number of patients with difficult-to-treat CRS were actually found in clusters associated with neutrophilic disease and elevated pro-inflammatory cytokines. The study also found that elevated levels of IL-10 were associated with less severe, more treatment-responsive disease⁴⁴.

CRS endotyping has the potential to impact patient care by identifying individuals with potentially recalcitrant disease and predicting treatment outcomes. A recent pilot study by Divekar *et al.* incorporated a simple, commercially available immunoassay to identify putative CRS inflammatory endotypes in an approach that ultimately could be incorporated into clinical practice⁴³. Tissue analysis of 41 different inflammatory mediators in 26 patients with CRS identified three groups characterized by Th1/Th17 cytokines (IL-17A, granulocyte-colony stimulating factor, IL-8, and IFN- γ), Th2 cytokines (IL-5, IL-9, IL-13, and eotaxin), and growth factors (platelet-derived growth factor and vascular endothelial growth factor), respectively. The comparatively smaller number of identified clusters was likely secondary to a small sample size, as the number and stability of clusters identified by unsupervised approaches are typically highly dependent on the number of both input variables and subjects. Whereas this and prior studies specifically analyzed sinonasal tissue, a recent prospective study by Turner *et al.*

identified putative inflammatory endotypes using mucus alone³³. This minimally invasive approach could be more efficiently incorporated into clinical practice and has the potential to assign patients to disease clusters without attaining tissue and prior to any surgical intervention. The authors assessed 18 different inflammatory mediators in 90 patients with CRS and identified six disease clusters. In that report, similar to others, most patients were assigned to a Th2-dominant cluster, a pro-inflammatory cluster with a neutrophilic signature, or clusters with low overall inflammatory burden. Most importantly, the study found that clusters were predictive of postoperative improvements in disease-specific quality-of-life scores.

Therapeutic implications

The studies outlined above suggest that identification and characterization of CRS endotypes ultimately could both improve our understanding of CRS pathophysiology and augment patient care. Although individual biomarkers have some ability to classify patients or predict outcomes, they generally lack the sensitivity and specificity required to characterize patients with such a heterogeneous inflammatory disease^{45–49}. New classes of biotherapeutics that target individual cytokines and inflammatory pathway components are becoming increasingly available, and the ability to identify patients who may benefit from such therapies will be an essential step toward a more personalized approach to care. Several humanized monoclonal antibodies developed primarily for the treatment of severe asthma—including mepolizumab (anti-IL-5), omalizumab (anti-IgE), and dupilumab (anti-IL-4/13 receptor)—appear to also have efficacy for the treatment of nasal polyposis^{50–53}. However, treatment response has been highly variable, suggesting a subgroup effect that may be endotype-driven. For example, a small randomized trial evaluating the efficacy of the humanized anti-IL-5 antibody reslizumab for the treatment of nasal polyposis resulted in a response in only half of patients who received treatment. However, it was noted that increased nasal IL-5 levels were highly predictive of treatment response⁵⁴. A similar therapeutic window has been noted for omalizumab, with efficacy in patients with CRS being moderately dependent on peripheral IgE levels^{50,55}. Characterization of CRS endotypes has also highlighted the need for novel and non-Th2-directed therapeutic interventions, particularly given that a minority of patients carry a strongly Th2-dominant immune signature. Pro-inflammatory neutrophilic inflammation identified in a large subset of patients may also represent a recalcitrant CRS subpopulation that could benefit from targeted therapies^{32,33,44}. Based on this

characteristic inflammatory signature, these patients would also be expected to be less responsive to topical or systemic corticosteroids, further highlighting the need for novel interventions in this group. It is further likely that the identification of uncharacterized CRS endotypes or unique immune signatures will lead to the recognition of novel mechanisms of disease and additional targeted therapies going forward.

Conclusions

Recent identification and characterization of inflammatory CRS endotypes have improved our understanding of CRS pathophysiology and highlighted an area in need of further investigation. Future studies will need to determine whether identified disease clusters truly represent unique endotypes or whether patients present along a continuum with features consistent with multiple endotypes or inflammatory pathways. The stability of disease clusters and endotypes over time will also need to be confirmed, as will their association with medical or surgical treatment. The role of CRS endotyping in clinical practice has

yet to be defined but likely has the potential to identify clinically relevant subgroups, guide personalized therapeutic algorithms, and predict outcomes.

Grant information

JHT has received grant support from the National Institutes of Health (NIH)/National Institute of Deafness and Communication Disorders and additional support from the NIH/National Institute of Allergy and Infectious Diseases. He receives salary and other support through NIH RO3 DC014809, L30 AI113795, and CTSA award UL1TR000445 from the National Center for Advancing Translational Sciences (NCATS). The manuscript contents are solely the responsibility of the authors and do not necessarily represent official views of the NCATS or the NIH.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

- Blackwell DL, Lucas JW, Clarke TC: **Summary health statistics for U.S. adults: national health interview survey, 2012.** *Vital Health Stat 10.* 2014; 260: 1–161. [PubMed Abstract](#)
- Schiller JS, Lucas JW, Peregoy JA: **Summary health statistics for u.s. Adults: national health interview survey, 2011.** *Vital Health Stat 10.* 2012; 256: 1–218. [PubMed Abstract](#)
- Dykewicz MS: **7. Rhinitis and sinusitis.** *J Allergy Clin Immunol.* 2003; 111(2 Suppl): S520–9. [PubMed Abstract](#) | [Publisher Full Text](#)
- Bhattacharyya N: **Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States.** *Ann Otol Rhinol Laryngol.* 2011; 120(7): 423–7. [PubMed Abstract](#) | [Publisher Full Text](#)
- Bachert C, Akdis CA: **Phenotypes and Emerging Endotypes of Chronic Rhinosinusitis.** *J Allergy Clin Immunol Pract.* 2016; 4(4): 621–8. [PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Kim DW, Cho SH: **Emerging Endotypes of Chronic Rhinosinusitis and Its Application to Precision Medicine.** *Allergy Asthma Immunol Res.* 2017; 9(4): 299–306. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Akdis CA, Bachert C, Cingi C, *et al.*: **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(6): 1479–90. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- De Greve G, Hellings PW, Fokkens WJ, *et al.*: **Endotype-driven treatment in chronic upper airway diseases.** *Clin Transl Allergy.* 2017; 7: 22. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Huang Z, Nayak JV, Sun Y, *et al.*: **Peripheral blood T-helper cells and eosinophil populations in patients with atopic and nonatopic chronic rhinosinusitis.** *Am J Rhinol Allergy.* 2017; 31(1): 8–12. [PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Watanabe S, Pinto JM, Bashir ME, *et al.*: **Effect of prednisone on nasal symptoms and peripheral blood T-cell function in chronic rhinosinusitis.** *Int Forum Allergy Rhinol.* 2014; 4(8): 609–16. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- O'Connell BP, Schlosser RJ, Wentzel JL, *et al.*: **Systemic monocyte-derived dendritic cells and associated Th2 skewing in chronic rhinosinusitis.** *Otolaryngol Head Neck Surg.* 2014; 150(2): 312–20. [PubMed Abstract](#) | [Publisher Full Text](#)
- Ba L, Zhang N, Meng J, *et al.*: **The association between bacterial colonization and inflammatory pattern in Chinese chronic rhinosinusitis patients with nasal polyps.** *Allergy.* 2011; 66(10): 1296–303. [PubMed Abstract](#) | [Publisher Full Text](#)
- Thienhaus ML, Wohlers J, Podschun R, *et al.*: **Antimicrobial peptides in nasal secretion and mucosa with respect to Staphylococcus aureus colonization in chronic rhinosinusitis with nasal polyps.** *Rhinology.* 2011; 49(5): 554–61. [PubMed Abstract](#)
- Soyka MB, Wawrzyniak P, Eiwegger T, *et al.*: **Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN- γ and IL-4.** *J Allergy Clin Immunol.* 2012; 130(5): 1087–1096.e10. [PubMed Abstract](#) | [Publisher Full Text](#)
- Basinski TM, Holzmann D, Eiwegger T, *et al.*: **Dual nature of T cell-epithelium interaction in chronic rhinosinusitis.** *J Allergy Clin Immunol.* 2009; 124(1): 74–80.e1-8. [PubMed Abstract](#) | [Publisher Full Text](#)
- Richer SL, Truong-Tran AQ, Conley DB, *et al.*: **Epithelial genes in chronic rhinosinusitis with and without nasal polyps.** *Am J Rhinol.* 2008; 22(3): 228–34. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ho J, Bailey M, Zaunders J, *et al.*: **Group 2 innate lymphoid cells (ILC2s) are increased in chronic rhinosinusitis with nasal polyps or eosinophilia.** *Clin Exp Allergy.* 2015; 45(2): 394–403. [PubMed Abstract](#) | [Publisher Full Text](#)
- Liao B, Cao PP, Zeng M, *et al.*: **Interaction of thymic stromal lymphopoietin, IL-33, and their receptors in epithelial cells in eosinophilic chronic rhinosinusitis with nasal polyps.** *Allergy.* 2015; 70(9): 1169–80. [PubMed Abstract](#) | [Publisher Full Text](#)
- Shaw JL, Fakhri S, Citardi MJ, *et al.*: **IL-33-responsive innate lymphoid cells are an important source of IL-13 in chronic rhinosinusitis with nasal polyps.** *Am J Respir Crit Care Med.* 2013; 188(4): 432–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lam EP, Kariyawasam HH, Rana BM, *et al.*: **IL-25/IL-33-responsive T_H2 cells characterize nasal polyps with a default T_H17 signature in nasal mucosa.** *J Allergy Clin Immunol.* 2016; 137(5): 1514–24. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Tan BK, Klingler AI, Poposki JA, *et al.*: **Heterogeneous inflammatory patterns in chronic rhinosinusitis without nasal polyps in Chicago, Illinois.** *J Allergy Clin Immunol.* 2017; 139(2): 699–703.e7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Zhang N, van Zele T, Perez-Novo C, *et al.*: **Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease.** *J Allergy Clin Immunol.* 2008; 122(5): 961–8. [PubMed Abstract](#) | [Publisher Full Text](#)
- Wang X, Zhang N, Bo M, *et al.*: **Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: A multicenter study in Europe, Asia, and Oceania.** *J Allergy Clin Immunol.* 2016; 138(5): 1344–53. [PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Zhang N, Holtappels G, Gevaert P, *et al.*: **Mucosal tissue polyclonal IgE is functional in response to allergen and SEB.** *Allergy.* 2011; 66(1): 141–8. [PubMed Abstract](#) | [Publisher Full Text](#)
- Bachert C, Gevaert P, Holtappels G, *et al.*: **Total and specific IgE in nasal polyps**

- is related to local eosinophilic inflammation. *J Allergy Clin Immunol.* 2001; 107(4): 607–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Hoddeson EK, Wise SK: **The Role of IgE Production in the Pathophysiology of Rhinitis and Rhinosinusitis.** *Curr Allergy Asthma Rep.* 2011; 11(3): 230–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. **F** Divekar R, Lal D: **Recent advances in biologic therapy of asthma and the role in therapy of chronic rhinosinusitis [version 1; referees: 2 approved].** *F1000Res.* 2018; 7: 412.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 28. **F** Pothoven KL, Norton JE, Suh LA, *et al.*: **Neutrophils are a major source of the epithelial barrier disrupting cytokine oncostatin M in patients with mucosal airways disease.** *J Allergy Clin Immunol.* 2017; 139(6): 1966–1978.e9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 29. **F** Wang H, Li ZY, Jiang WX, *et al.*: **The activation and function of IL-36 γ in neutrophilic inflammation in chronic rhinosinusitis.** *J Allergy Clin Immunol.* 2018; 141(5): 1646–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 30. van Zele T, Claeys S, Gevaert P, *et al.*: **Differentiation of chronic sinus diseases by measurement of inflammatory mediators.** *Allergy.* 2006; 61(11): 1280–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. van Bruene N, Pérez-Novo CA, Basinski TM, *et al.*: **T-cell regulation in chronic paranasal sinus disease.** *J Allergy Clin Immunol.* 2008; 121(6): 1435–41, 1441.e1-3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. **F** 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; 137(5): 1449–1456.e4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 33. Turner JH, Chandra RK, Li P, *et al.*: **Identification of clinically relevant chronic rhinosinusitis endotypes using cluster analysis of mucus cytokines.** *J Allergy Clin Immunol.* 2018; 141(5): 1895–1897.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 34. Stevens WW, Ocampo CJ, Berdnikovs S, *et al.*: **Cytokines in Chronic Rhinosinusitis. Role in Eosinophilia and Aspirin-exacerbated Respiratory Disease.** *Am J Respir Crit Care Med.* 2015; 192(6): 682–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 35. **F** Dennis SK, Lam K, Luong A: **A Review of Classification Schemes for Chronic Rhinosinusitis with Nasal Polyposis Endotypes.** *Laryngoscope Investig Otolaryngol.* 2016; 1(5): 130–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 36. Lal D, Scianna JM, Stankiewicz JA: **Efficacy of targeted medical therapy in chronic rhinosinusitis, and predictors of failure.** *Am J Rhinol Allergy.* 2009; 23(4): 396–400.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. **F** Bachert C, Zhang N, Hellings PW, *et al.*: **Endotype-driven care pathways in patients with chronic rhinosinusitis.** *J Allergy Clin Immunol.* 2018; 141(5): 1543–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 38. Salomon MV, Bottini R, de Souza Filho GA, *et al.*: **Bacteria isolated from roots and rhizosphere of *Vitis vinifera* retard water losses, induce abscisic acid accumulation and synthesis of defense-related terpenes in *in vitro* cultured grapevine.** *Physiol Plant.* 2014; 151(4): 359–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. **F** Hinks TS, Brown T, Lau LC, *et al.*: **Multidimensional endotyping in patients with severe asthma reveals inflammatory heterogeneity in matrix metalloproteinases and chitinase 3-like protein 1.** *J Allergy Clin Immunol.* 2016; 138(1): 61–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 40. **F** Silkoff PE, Laviolette M, Singh D, *et al.*: **Identification of airway mucosal type 2 inflammation by using clinical biomarkers in asthmatic patients.** *J Allergy Clin Immunol.* 2017; 140(3): 710–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 41. **F** Peters MC, Mekonnen ZK, Yuan S, *et al.*: **Measures of gene expression in sputum cells can identify T_H2-high and T_H2-low subtypes of asthma.** *J Allergy Clin Immunol.* 2014; 133(2): 388–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 42. **F** Howrylak JA, Moll M, Weiss ST, *et al.*: **Gene expression profiling of asthma phenotypes demonstrates molecular signatures of atopy and asthma control.** *J Allergy Clin Immunol.* 2016; 137(5): 1390–1397.e6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 43. **F** Divekar R, Rank M, Squillace D, *et al.*: **Unsupervised network mapping of commercially available immunoassay yields three distinct chronic rhinosinusitis endotypes.** *Int Forum Allergy Rhinol.* 2017; 7(4): 373–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 44. **F** Liao B, Liu JX, Li ZY, *et al.*: **Multidimensional endotypes of chronic rhinosinusitis and their association with treatment outcomes.** *Allergy.* 2018; 73(7): 1459–69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 45. Turner JH, Li P, Chandra RK: **Mucus T helper 2 biomarkers predict chronic rhinosinusitis disease severity and prior surgical intervention.** *Int Forum Allergy Rhinol.* 2018; 8(10): 1175–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 46. **F** Ninomiya T, Noguchi E, Haruna T, *et al.*: **Periostin as a novel biomarker for postoperative recurrence of chronic rhinosinitis with nasal polyps.** *Sci Rep.* 2018; 8(1): 11450.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 47. **F** Maxfield AZ, Landegger LD, Brook CD, *et al.*: **Periostin as a Biomarker for Nasal Polyps in Chronic Rhinosinusitis.** *Otolaryngol Head Neck Surg.* 2018; 158(1): 181–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 48. **F** Jonstam K, Westman M, Holtappels G, *et al.*: **Serum periostin, IgE, and SE-IgE can be used as biomarkers to identify moderate to severe chronic rhinosinusitis with nasal polyps.** *J Allergy Clin Immunol.* 2017; 140(6): 1705–1708.e3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 49. **F** Chen F, Hong H, Sun Y, *et al.*: **Nasal interleukin 25 as a novel biomarker for patients with chronic rhinosinusitis with nasal polyps and airway hypersensitivity: A pilot study.** *Ann Allergy Asthma Immunol.* 2017; 119(4): 310–316.e2.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 50. Chandra RK, Clavenna M, Samuelson M, *et al.*: **Impact of omalizumab therapy on medication requirements for chronic rhinosinusitis.** *Int Forum Allergy Rhinol.* 2016; 6(5): 472–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 51. **F** 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(1): 110–6.e1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 52. **F** Bachert C, Sousa AR, Lund VJ, *et al.*: **Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial.** *J Allergy Clin Immunol.* 2017; 140(4): 1024–1031.e14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 53. **F** 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(5): 469–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 54. Gevaert P, Lang-Loidolt D, Lackner A, *et al.*: **Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps.** *J Allergy Clin Immunol.* 2006; 118(5): 1133–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
 55. Clavenna MJ, Turner JH, Samuelson M, *et al.*: **Differential effect of omalizumab on pulmonary function in patients with allergic asthma with and without chronic rhinosinusitis.** *Allergy Asthma Proc.* 2016; 37(1): 23–6.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. Zheng Liu

Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Competing Interests: No competing interests were disclosed.

2. Murugappan Ramanathan Jr

Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research