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Chronic Rhinosinusitis Phenotypes: An Approach to Better Medical Care for Chronic Rhinosinusitis

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The review articles in *The Journal of Allergy and Clinical Immunology: In Practice* focus on phenotypes of chronic rhinosinusitis (CRS), one of the most common diseases in the United States and other countries of the world. How did interest in CRS phenotypes come about? First, the senior author, Richard F. Lockey, MD, has always believed that CRS is primarily a medical disease, one that necessitates a complete history and physical examination to identify the comorbid and preexisting conditions that are related to or predispose to this disease. Second, just as asthma is not one disease, so too, CRS is not one disease. Identifying phenotypes will lead to a more appropriate diagnosis and treatment regimen. Third, the availability of rhinolaryngoscopy, a simple and vital modern-day diagnostic tool, enables any physician, regardless of the specialty, to confirm and treat this disease. The editorial leadership of *The Journal of Allergy and Clinical Immunology: In Practice* agreed with this concept, and Dr Lockey elicited the collaboration of Dr Seong Cho, a University of South Florida fellow faculty member, and Dr Claus Bachert, both of whom are clinicians who do CRS basic research. The definitions of CRS phenotypes will precede the definitions of various CRS endotypes. Both concepts will lead to better care of patients with this chronic disease.

An estimated prevalence of CRS is 5% to 15% of the adult population^{1–5} and costs the health care system in the United States approximately \$8 billion per year.⁶ CRS also significantly affects the quality of life in some symptom domains even more so than do other chronic diseases, such as angina and back pain.⁷ However, there is a tremendous gap between scientific evidence, that is, the lack of good quality CRS clinical and translational studies versus clinical practice. Stepwise approaches for the diagnosis and treatment of CRS, similar to guidelines for asthma, have not been validated and need to be established. The European position paper on rhinosinusitis and nasal polyps guidelines show stepwise approaches according to the severity of disease, but these have not been validated.⁸ Much of

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the lack of knowledge about CRS leads to a misconception by most physicians that CRS is primarily a surgical versus a medical disease. This editorial outlines the authors' approach to CRS using the information obtained from the literature and the international experts in this series of articles that define various CRS phenotypes.

DEFINITION OF CRS

What is CRS? One definition of CRS is that it is an inflammatory condition of the nose and paranasal sinuses persisting for at least 12 weeks characterized by 2 or more nasal/sinus symptoms, one of which includes nasal obstruction or nasal discharge $\pm$ facial pressure/pain and $\pm$ reduced smell.⁸ In addition, endoscopic signs of mucopurulent discharge or edematous/mucosal obstruction of the middle meatus or radiologic abnormalities, such as mucosal changes within the ostiomeatal complex or sinuses, support the diagnosis. As the definition indicates, CRS is a chronic inflammatory disease of the mucosal membranes of the upper airway just as are asthma and chronic obstructive pulmonary disease, chronic inflammatory diseases of the lower airway. The definition itself as well as the clinical presentation of CRS indicates that it is primarily a medical problem. Defining CRS phenotypes is a critical step in determining optimal medical or surgical treatment.

DIFFERENTIAL DIAGNOSIS AND COMORBID/COEXISTING CONDITIONS

A detailed history and physical examination is the ideal approach for any patient with any disease, and in this case, so too with CRS. It should include all the presenting symptoms and signs associated with CRS. Some of these include discolored nasal discharge from the nares or into the posterior pharynx, facial discomfort, pain in the maxilla, foul smell or taste, rhinorrhea, postnasal drip, nasal stuffiness, lethargy, fatigue, and others. Likewise, coexisting and comorbid conditions or diseases, which present with some of the same symptoms of CRS, must be addressed. An example of the latter is a patient referred for "sinus headaches." However, the etiology of these headaches may be temporomandibular joint dysfunction, tension headaches, or secondary to a neurologic problem, not CRS. Allergic and nonallergic rhinitis can predispose to CRS and must be considered as a confounding problem in evaluating patients with this disease. Laryngopharyngeal reflux disease/gastroesophageal reflux disease can also predispose or occur concomitantly with CRS. A globus sensation associated with laryngopharyngeal reflux disease/gastroesophageal reflux disease can often be confused with some of the presenting symptoms of CRS, that is, laryngopharynx clearing ("throat clearing") and "postnasal drip." Certain medical conditions also predispose to CRS, often times overlooked by clinicians. Some of these include primary and secondary immunodeficiency diseases, cystic fibrosis, mucociliary dysfunction, drug abuse, and various types of rhinitis.

IDENTIFICATION OF CRS PHENOTYPES

The identification of a given CRS phenotype (Table I) is primarily based on the clinical evaluation; for example, does the patient have chronic rhinosinusitis with nasal polyps (NPs) (CRSwNP) or chronic rhinosinusitis without nasal polyps (CRSsNP)? If they have polyps, do nonsteroidal inflammatory drugs exacerbate their respiratory disease? Is their CRS

infectious? If so, is it associated with underlying medical problems? Is the etiology fungal in origin? Likewise, some CRS is associated with anatomic abnormalities or congenital diseases such as immotile cilia syndrome and cystic fibrosis. In addition to phenotyping CRS, endotyping CRS with various biomarkers should become more possible in the future as endotypes are better defined, that is, eosinophilic versus neutrophilic CRS.

Essential to phenotyping CRS is rhinolaryngoscopy. A competent rhinoscopic examination is essential to diagnose the CRS phenotype. Anterior rhinoscopy (via the anterior nares) visualizes at best only the first one-third of the nasal cavity and is inadequate to visualize the posterior naso-oral or laryngeal pharynx. Rhinolaryngoscopy is a simple and inexpensive procedure and should be performed routinely in patients suspected of any persistent upper airway problem, in particular, CRS. Just as office spirometry is a routine procedure to assist in the diagnosis of asthma, so too should rhinolaryngoscopy be used on a regular basis for CRS.

Other confirmatory diagnostic tools to help phenotype CRS can include *in vivo* and *in vitro* IgE tests, an aspirin challenge to rule in or rule out aspirin-exacerbated respiratory disease, and a screening immunologic evaluation, in particular, immunoglobulin levels and specific antibody titers. In addition, a sweat chloride and a nasomucosal biopsy may be indicated. Patients refractory to therapy may need an additional evaluation to define the underlying pathophysiological mechanisms causing the disease. For example, a long-term macrolide antibiotic treatment for patients with CRSsNP can be more effective in those who have normal IgE versus abnormal IgE levels.⁹ Defining whether the inflammation is eosinophilic versus neutrophilic can also predict prognosis and help guide a treatment plan. For example, there is a significant age-related decline in eosinophilic inflammation with an increased prevalence of NPs and comorbid asthma in subjects with CRS as reported in a US cohort.¹⁰ Another example is that elderly versus nonelderly Asian subjects with noneosinophilic NPs had better endoscopic scores at 12 months following surgery.¹¹ As previously indicated, endotyping airway diseases are just now becoming a reality. This is illustrated by the number of biologics available or now under investigation to treat severe asthma. The same biologics have been used in small clinical trials in patients with CRSwNP with efficacy. The topic of endotyping and biologics is discussed below.

OPTIMAL USE OF IMAGING STUDIES

A computed tomography (CT) scan can be vital to diagnose or treat CRS. However, the overuse or misuse of imaging techniques is a major problem in modern medicine. A CT scan of the sinuses should be obtained primarily when rhinolaryngoscopy indicates structural abnormalities as a suspected cause of CRS or other complications from CRS are suspected. Structural abnormalities, such as concha bullosa, Haller cell, and paradoxical middle turbinate abnormalities, usually do not cause CRS. If they did, CRS theoretically would be more common in younger individuals because these structural abnormalities are present since childhood. A CT also is most useful when adequate and prolonged medical therapy has failed and surgery is contemplated. A *New England Journal of Medicine* article discusses an increasing concern for the overuse of CT scans as an important source of radiation exposure and increased cancer risk.¹² It concludes that there is direct evidence from epidemiologic

studies that the organ doses from 2 or 3 CT scans result in radiation doses in the range of 30 to 90 mSv. This may result in an increased risk of cancer for both adults and children. The authors have seen children who have had 2 or 3 CT scans of their head in the first 5 years of life in the process of evaluating them for CRS, CRS surgery, and postoperative follow-up. Likewise, the authors are concerned that surgery for CRS has become so much more common for children than it was even 20 years ago, when almost all children with chronic sinusitis were treated medically. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines indicate that surgery of the sinuses is rarely indicated for children, with the exception of CRS in patients with cystic fibrosis.⁸ Additional concern is that CT scans, when they are obtained, are frequently overinterpreted by radiologists and physicians. For example, a CT scan report often states “Mucosal thickening in the right and left maxillary sinuses compatible with sinusitis.” This automatically triggers the physician to think that the patient has “CRS,” not knowing that a common cold, allergic rhinitis, and just plain mucosal cysts or membrane scarring can account for these changes. This over-interpretation leads to excessive treatment for some individuals who do not have other symptoms and signs of CRS and only have a CT scan with so-called mucosal thickening.

OPTIMAL USE OF GLUCOCORTICOSTEROIDS

Clinical guidelines for step-up or step-down doses of inhaled corticosteroids are established to treat asthma. However, dose-response studies are lacking in CRS. This may be due to limited and ineffective distribution of intranasal corticosteroids (INCSs), especially in those with severe nasomucosal edema or large NPs. Overcoming this limitation may play a major role in the successful topical use of INCSs for CRS. For example, one clinical trial shows that INCSs with a mucosal atomized device may provide better results than a standard nasal spray device.¹³ Another example of an innovative device is a “bidirectional breath powered” drug delivery system. Initial double-blind and randomized clinical trials performed with this device indicate that recalcitrant CRSsNP responds to high-dose fluticasone treatment.¹⁴ However, only 20 adult subjects were enrolled in this study. A multicentered randomized, double-blind, placebo-controlled phase III trial of 323 patients with NPs from 5 countries demonstrates a statistically significant difference in core symptoms of CRS and endoscopically measured polyp size reduction, in some cases, even eliminating NP.¹⁵ Advanced intranasal drug delivery systems should provide a more reliable method to see a dose response of INCSs and to further assess the importance of step-up or step-down treatment in patients with this disease. Each study of this kind should indicate whether or not there are significantly more side effects with higher doses of INCSs. Predictably, the side effects should be much less than with systemic glucocorticoids, a treatment temporarily used for patients with CRS. One other area for improvement, or at least additional research, is the combined use of topical INCSs plus other medications, particularly a topical decongestant. In fact, nasal stuffiness is usually the symptom that is most bothersome to patients with any type of upper airway disease. Two studies indicate that oxymetazoline does not cause “rebound phenomenon” as long as it is used with INCSs.^{16,17} Reduction of mucosal edema by the use of topical decongestants seems reasonable and should enhance delivery of INCSs.

OPTIMAL USE OF ANTIBIOTICS

Antibiotics can be effective for some patients with CRS, at least in treating acute exacerbations. However, there is no evidence-based study about the optimal duration of antibiotic treatment for CRS. Most clinicians use antibiotics for 2 to 4 weeks. In the authors' experience, there are significant individual responses to antibiotics. Therefore, we recommend that antibiotics be continued for 7 to 10 days beyond the time the patient becomes asymptomatic, that is, has no additional mucopurulent discharge. If they do not show a response to antibiotic therapy for 1 week to 10 days, an endoscopic-guided sinus culture may be indicated. Culturing nasal secretion is a low-yield process, whereas visual observation and endoscopy-guided collection of pus is more ideal to identify the causative organism. Again, rhinolaryngoscopy becomes invaluable, not only to diagnose but also to optimize antibiotic treatment.

Long-term antibiotic therapy (usually 12 weeks) with macrolides in both CRSsNP and CRSwNP, and doxycycline in CRSwNP appears to be effective for some patients. However, optimizing dosing strategy and duration needs to be better established by appropriate long-term studies of each of these 2 phenotypes. Bacterial resistance due to overuse of macrolides is a complication of such therapy.¹⁸

USE OF BIOLOGIC AGENTS BASED ON ENDOTYPING

There are various clinical trials in patients with CRSwNP using omalizumab (anti-IgE),¹⁹ reslizumab (anti-IL-5),²⁰ mepolizumab (anti-IL-5),²¹ and dupilumab (anti-IL-4R α).²² A randomized, double-blind, placebo-controlled multicenter study of dupilumab among adults with CRSwNP was conducted at 13 sites in the United States and Europe and published in 2016.²² The addition of subcutaneous dupilumab to INCSs compared with INCSs alone significantly reduced the NP score and the Lund-Mackay CT score. It also improved the sinonasal symptom score and sense of smell after 16 weeks of treatment. This trial of 60 subjects, 30 placebo and 30 dupilumab, is the largest CRS biological study done to date. The relatively small size of the study makes a subgroup analysis based on biomarkers and response to treatment difficult. However, it shows some promising results.

One of the most consistent outcomes in asthma clinical trials with biologic agents such as omalizumab, mepolizumab, reslizumab, and dupilumab is that patients with asthma with high blood eosinophil counts and T_H2 cytokines respond better than do those with low or normal blood eosinophil counts and T_H2 cytokines. There is no clear-cut evidence that these same serum biological markers will be useful biomarkers for CRS. This may be explained by the fact that CRS is more of a mucosal membrane disease than a systemic disease in which blood eosinophilia usually does not occur. The fact that CRS appears to be more of a localized mucosal rather than systemic disease may make endotyping CRS more difficult. In the past, nasal cytology was routine in patients with upper airway diseases. It may be a procedure that needs to be revisited. Measuring cytokines in nasal secretions may facilitate future endotyping of this disease as demonstrated in early CRS trials with reslizumab.²⁰

The use of biologics for asthma has led the way and should give many clues to those designing studies of various phenotypes/endotypes of CRS. There are both neutrophilic and eosinophilic endotypes of asthma as there are for CRS. In fact, many Asian CRSwNP are neutrophilic,¹¹ that is, have an excessive number of neutrophils in sinonasal tissues and nasal secretions. Developing biologic agents to target neutrophilic CRS seems reasonable.

STEPWISE APPROACH?

Once CRS is diagnosed and the phenotype identified, a proper management program should be established. A stepwise management program for asthma has been established on the basis of numerous clinical trials. However, such trials are lacking for CRS, which is somewhat surprising for such a common and important chronic disease. Table II outlines a simplified stepwise treatment approach to patients who present with CRS after ruling out atypical phenotypes such as allergic fungal sinusitis or CRS associated with cystic fibrosis. This is not based on good quality randomized trials; it is a suggested approach based on limited clinical evidence.

In conclusion, this series of articles on CRS phenotypes is just a beginning. All CRS is not the same nor does it have the same pathophysiology; phenotypes first, endotypes second, and new treatments third. Hopefully, a multitude of advances, similar to those that have occurred in the treatment of asthma, will take place in the future for the medical management of CRS.

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References

1. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. *Vital Health Stat.* 2009; 10(242):1–157.
2. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy.* 2012; 67:91–8. [PubMed: 22050239]
3. Shi JB, Fu QL, Zhang H, Cheng L, Wang YJ, Zhu DD, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. *Allergy.* 2015; 70:533–9. [PubMed: 25631304]
4. Kim YS, Kim NH, Seong SY, Kim KR, Lee GB, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in Korea. *Am J Rhinol Allergy.* 2011; 25:117–21. [PubMed: 21679523]
5. Pilan RR, Pinna FR, Bezerra TF, Mori RL, Padua FG, Bento RF, et al. Prevalence of chronic rhinosinusitis in Sao Paulo. *Rhinology.* 2012; 50:129–38. [PubMed: 22616073]
6. DeMarcantonio MA, Han JK. Nasal polyps: pathogenesis and treatment implications. *Otolaryngol Clin North Am.* 2011; 44:685–95. [PubMed: 21621054]
7. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg.* 1995; 113:104–9. [PubMed: 7603703]

8. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012: a summary for otorhinolaryngologists. *Rhinology*. 2012; 50:1–12. [PubMed: 22469599]
9. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope*. 2006; 116:189–93. [PubMed: 16467702]
10. Cho SH, Hong SJ, Han B, Lee SH, Suh L, Norton J, et al. Age-related differences in the pathogenesis of chronic rhinosinusitis. *J Allergy Clin Immunol*. 2012; 129:858–60. [PubMed: 22236731]
11. Kim DW, Kim DK, Jo A, Jin HR, Eun KM, Mo JH, et al. Age-related decline of neutrophilic inflammation is associated with better postoperative prognosis in non-eosinophilic nasal polyps. *PLoS One*. 2016; 11:e0148442. [PubMed: 26849431]
12. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med*. 2007; 357:2277–84. [PubMed: 18046031]
13. Neubauer PD, Schwam ZG, Manes RP. Comparison of intranasal fluticasone spray, budesonide atomizer, and budesonide respules in patients with chronic rhinosinusitis with polyposis after endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2016; 6:233–7. [PubMed: 26679480]
14. Hansen FS, Djupesland PG, Fokkens WJ. Preliminary efficacy of fluticasone delivered by a novel device in recalcitrant chronic rhinosinusitis. *Rhinology*. 2010; 48:292–9. [PubMed: 21038019]
15. OptiNose. [Accessed April 29, 2016] OptiNose announces positive results of second phase III pivotal trial for OPN-375. 2015. Press release Available from: <http://www.optinose.com/press-releases/optinose-announces-positive-results-of-second-phase-iii-pivotal-trial-for-opn-375>
16. Rael EL, Ramey J, Lockey RF. Oxymetazoline hydrochloride combined with mometasone nasal spray for persistent nasal congestion (pilot study). *World Allergy Organ J*. 2011; 4:65–7. [PubMed: 23283177]
17. Thongngarm T, Assanasen P, Pradubpongsa P, Tantilipikorn P. The effectiveness of oxymetazoline plus intranasal steroid in the treatment of chronic rhinitis: a randomised controlled trial. *Asian Pac J Allergy Immunol*. 2016; 34:30–7. [PubMed: 26994623]
18. Bachert C, Hamilos DL. Are antibiotics useful for chronic rhinosinusitis? *J Allergy Clin Immunol Pract*. 2016; 4:629–38. [PubMed: 26969267]
19. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013; 131:110–6. [PubMed: 23021878]
20. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol*. 2006; 118:1133–41. [PubMed: 17088140]
21. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol*. 2011; 128:989–95. [PubMed: 21958585]
22. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016; 315:469–79. [PubMed: 26836729]

TABLE I**CRS phenotypes**

1. CRSsNP
2. CRSwNP
3. CRS with aspirin-exacerbated respiratory disease
4. Allergic fungal sinusitis
5. Infectious CRS
6. CRS with cystic fibrosis
7. Other CRS phenotypes
a. CRS with immune deficiencies such as common variable immunodeficiency and specific antibody deficiency
b. CRS with immotile cilia syndrome
c. CRS with anatomical abnormalities
d. Biomarker based (endotypes)
1) Eosinophilic CRS vs noneosinophilic CRS
2) Allergic CRS vs nonallergic CRS
3) T _H 2 high vs T _H 2 low
4) High IgE vs normal IgE

TABLE II

Stepwise approach in management of CRS *

1. INCSs ± short-term antibiotics for acute exacerbation
2. INCSs and topical decongestant ± endoscopy-guided culture-based antibiotics for acute exacerbation
3. Adding higher dose of INCSs or a better delivery system of INCSs
4. Adding long-term antibiotics: macrolide for CRSsNP and CRSwNP or doxycycline for CRSwNP
5. Adding biologic agents. Until the Food and Drug Administration approves biologic agents for CRS, biologic agents can be used in CRS with comorbid moderate to severe asthma
6. Surgery in medical treatment failure or other phenotypes such as antrochoanal polyps, allergic fungal sinusitis, or CRS with cystic fibrosis

* Other treatments such as high-volume nasal saline irrigation can also be used in any step.

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