Immunorhinology and rhinosinusitis: Where are we heading?

Over the past 2 decades, multiple etiologic options have been published as to the cause of chronic rhinosinusitis (CRS). We have had excellent documents that relate to microbiologic organisms, including viruses, bacteria, and fungi. These have taken the form of a multitude of different pathologic entities, including immunologic response to fungi and bacteria, staph exotoxin, and bacterial biofilm, and, more recently, the importance of the microbiome. However, we are still left without any single etiologic factor involved in the development of CRS. This edition of the American Journal of Rhinology and Allergy has a number of extremely fascinating themes.

The first theme is aimed at highlighting the sinonasal microbiome in CRS and potential factors in the stimulation of the inflammatory process. Anderson et al. performed a systematic review of the sinonasal microbiome in CRS, and their findings indicated that, in fact, there is no clear single causative microbe. There was significant heterogeneity throughout their studied articles, with firmicutes, Actinobacteria, and bacteroides being identified in both the controls and the patients with CRS. There is clearly much more research required to fully define the role that the microbiome plays in CRS. In terms of factors that influence the inflammatory cycle, Shimizu et al. define the role that the microbiome plays in CRS. In terms of factors that influence the inflammatory cycle, Shimizu et al. defined the role that the microbiome plays in CRS. In terms of factors that influence the inflammatory cycle, Shimizu et al. defined the role that the microbiome plays in CRS. In terms of factors that influence the inflammatory cycle, Shimizu et al. defined the role that the microbiome plays in CRS. In terms of factors that influence the inflammatory cycle, Shimizu et al. defined the role that the microbiome plays in CRS. In terms of factors that influence the inflammatory cycle, Shimizu et al. defined the role that the microbiome plays in CRS.

Fascinating articles that looked at the role that alarmins play in the pathogenesis of upper airway inflammation. They specifically looked at alarmin protein high mobility group box 1 (HMGB1). With sound methodology, they found significantly higher concentrations of HMGB1 in nasal secretions from patients with CRSwNP or with allergic rhinitis (AR) compared with the control. They noted that TNF-α stimulated the production of HMGB1, which, in turn, upregulated the production and secretion of interleukins 6 and 8, which indicated that HMGB1 does in fact play an important role in the pathogenesis of upper airway inflammation.

Lee et al. looked at the role of a number of cytokines in the nasal epithelium of patients with AR, and they showed that a decreased expression of epithelial junctional protein was found in patients with AR, with disruption of epithelial integrity via interleukins 4 and 5, and TNF-α, which indicated a possible role in the pathogenesis of AR. There are also valuable data from Shun et al. who evaluated the role that hypoxia plays in the formation of nasal polyposis by promoting autophagy in nasal polyp fibroblasts. The autophagy seems to be suppressed in hypoxia through the antiglycolytic activity of SIRT6, which is shown to be beneficial to nasal polyp formation. There are significant potential therapeutic benefits in the management of nasal polyposis if glucose metabolism through a SIRT6-based strategy can be found to be modulated.

AR has long fascinated researchers and clinicians. The relationship between AR and asthma is well known. It, therefore, was interesting to see the article from Dogru that showed that asthma comorbidity had no effect on the severity of AR. It, however, was shown that the majority of children with AR, in fact, do have asthma comorbidity and should be investigated for it. Utilizing our knowledge of the asthma literature and the well-documented role that reactive oxygen species play in the pathogenesis of asthma, Ulusoy et al. aimed to investigate thiol-disulfide homeostasis, a new oxidative stress marker in seasonal AR. They found, that seasonal AR elevates systemic oxidative stress and reduces antioxidant enzyme activities which may aid us in future therapies of this condition. AR has also been related to attention-deficit/hyperactivity disorder (ADHD), and Yang et al. performed a prospective study that looked at the treatment response in terms of ADHD-like symptoms from AR therapy. This previously unresearched area showed high ADHD scores in children with AR compared with the healthy controls, and these scores decreased significantly with the treatment of AR. They concluded that children who had borderline ADHD symptoms should have their AR appropriately treated before instituting ADHD therapies.

There also is an excellent article about CRS and its relationship to the other known effects of chronic inflammation, such as endothelial dysfunction and atherosclerosis. It is notable that there is a strong association between endothelial dysfunction and atherosclerosis was found in patients with CRS. It also is worth noting that other inflammatory diseases, e.g., asthma, are often undiagnosed in patients with CRS. The study performed by Frensda et al. showed the high frequency of asthma in patients with CRS, and, much like the study by Dogru, indicated a need for upper-airway physicians to be cognizant and investigate for the presence of lower airway disorder. Xiang et al. evaluated the role for house-dust mite allergen extract subcutaneous immunotherapy and its response in China. They found very good safety and effectiveness in the treatment of both AR and asthma, and that, along with other medical approaches, immunotherapy should be considered.

The prevalence of AR differs significantly throughout the world, and Kim et al. investigated both the prevalence and sensitivity of allergens in Korean children with AR. They found that the prevalence in children was nearly 21%. House-dust mite was still by far the most common allergen group, at 87.3%, and pollens, molds, and house dust mites at 37%, 12.4%, and 8.4%, respectively, were found to make up the balance. Freitas et al. looked at risk factors and rhinitis in children in the Amazon and found that, although a genetic background was a significant risk factor in both a rural island and an urban island population, the role of environmental exposure associated with lifestyle changes was predominant in the group on the urban island, which confirmed other publications that indicated a role of environmental exposure in the urban setting in the development of AR.

A second theme of this edition of the American Journal of Rhinology and Allergy was to assess advancing surgical approaches and the most-effective surgical technique for varying pathology. The article by El-Anwar et al. evaluated varying techniques for repair of bilateral choanal atresia. They showed that an endoscopic repair with resection of the posterior portion of the vomer and without the need for stenting was effective and surgically simpler, with good long-term results in a large group of patients. Lin et al. from the Massachusetts Eye and Ear Infirmary, compared varying techniques of medial rectus muscle retraction for endoscopic exposure of the medial intraconal space. This article is extremely valuable given the rapidly advancing field of endoscopic
orbital surgery. The investigators described four different surgical approaches, including external medial rectal muscle retraction, transseptal retraction by using a vessel loop, transcaonal retraction of the muscle by using a vessel loop, and transseptal four-handed technique by using a double-ball retraction by a second surgeon. It was fascinating to note that the external approach actually provided the worst exposure. The transseptal and the transseptal double-ball groups had the greatest exposure without any statistically significant difference between the two groups. This will have significant implications in our surgical approach to the orbit into the future.

The use of the nasofrontal beak as a landmark for superior septectomy during a Draf III drillout procedure was evaluated by Craig et al. They showed that the posterior edge of the nasofrontal beak can be used as a reliable landmark to avoid iatrogenic CSF during the superior septectomy.

Novel treatment approaches have also been studied in this issue of *American Journal of Rhinology and Allergy* with an article by Kirtsreesakul et al., who evaluated whether or not oxymetazoline would increase the efficacy of nasal steroids (INCS) in treating nasal polyps. They actually found that the use of the INCS was more effective over a 6-week period when used with oxymetazoline than when used alone. A meta-analysis of RCTs that looked at INCS in the treatment of obstructive sleep apnea was undertaken by Liu et al. and showed that patients who received intranasal corticosteroid therapy had a significant improvement in obstructive sleep apnea. Unfortunately, their meta-analysis was limited by the heterogeneity of the RCTs evaluated. This, however, does stimulate the discussion of the role of INCS in these patients.

A well-performed basic science study that looked at the “Protective effects of melatonin and selenium against apoptosis of olfactory sensory neurons: A rat model study” was undertaken by Koc et al. This well-conducted study indicated the possibility that supplementation of these two antioxidant agents for the treatment of CRS may reduce or even prevent anosmia. Clinical trials will clearly be required in this regard.

Postendoscopic sinus surgical bleeding is always an area of concern for the rhinologist. Kim et al. investigated whether the use of electrocauterization without any packing could be comparable with packing for control of postoperative hemorrhage, and they showed that there were comparable results between both the groups and that there was justification in electrocautery without packing technique in the management of patients who had FESS. The time honored effect of cold packs for postoperative bleeding and pain was also evaluated by Hirunwiwatkul et al. They, surprisingly, found that the use of a cold pack after turbinate and/or septal surgery had no real benefit in INCS in these patients.

Although the concept of the nasal valve in the causation of nasal obstructive symptoms is well understood, the correlation of the symptoms of obstruction, nasal airflow dynamics, and endoscopic appearance of the anatomic cross-sectional area of the nasal valve is poorly understood. A study by Bhatia et al. looked at the two-dimensional qualitative endoscopic assessment of the nasal valve and its value. They found that, although the qualitative assessment may help clinicians predict nasal valve dysfunction, the simple two-dimensional measures seem to be of limited value in accurately assessing the three-dimensional nasal valve quantitatively. More objective measures, including nasal airway resistance via rhinomanometry and acoustic rhinometry–derived minimum cross-sectional area, were more accurate.

Finally, an excellent article that reviewed dermatologic conditions of the nose was performed by Yigider et al., which comprehensively reviewed the main nasal skin lesions types and the available treatment strategies. They clinically classified these lesions as benign, premalignant, or malignant, and appropriately concluded that, due to the heterogeneity of these lesions, education by clinical otolaryngologists is mandatory.

On behalf of the *American Journal of Rhinology and Allergy* editorial board, I feel assured that the readership will find this issue of *American Journal of Rhinology and Allergy* extremely educational and highly useful in clinical practice. The worldwide distribution of both the authorship and readership of this journal makes it highly relevant and interesting. I trust that you will gain tremendously from this issue and have no doubt that these articles will be cited on multiple occasions in the years to come.

REFERENCES

1. Anderson M, Stokken J, Sanford T, et al. A systematic review of the sinonasal microbiome in chronic rhinosinusitis. Am J Rhinol Allergy 30:161–166, 2016.

2. Shimizu S, Kouzaki H, Kato T, et al. HMGB1-TLR4 signaling contributes to the secretion of interleukin 6 and interleukin 8 by nasal epithelial cells. Am J Rhinol Allergy 30:167–172, 2016.

3. Lee HJ, Kim B, Im NR, et al. Decreased expression of E-cadherin and ZO-1 in the nasal mucosa of patients with allergic rhinitis: Altered regulation of E-cadherin by IL-4, IL-5, and TNF-α. Am J Rhinol Allergy 30:173–178, 2016.

4. Shun CT, Lin SK, Hong CY, et al. Sirtuin 6 modulates hypoxia-induced autophagy in nasal polyp fibroblasts via inhibition of glycolysis. Am J Rhinol Allergy 30:179–185, 2016.

5. Dogru M. Investigation of asthma comorbidity in children with different severities of allergic rhinitis. Am J Rhinol Allergy 30:186–189, 2016.

6. Ulusoy S, Ayan NN, Dinc ME, et al. A new oxidative stress marker for thio-disulphide homeostasis in seasonal allergic rhinitis. Am J Rhinol Allergy 30:e53–e57, 2016.

7. Yang MT, Chen CC, Lee WT, et al. Attention-deficit/hyperactivity disorder-related symptoms improved with allergic rhinitis treatment in children. Am J Rhinol Allergy 30:209–214, 2016.

8. Elcioglu OC, Afsar B, Baka A, et al. Chronic rhinosinusitis, endothelial dysfunction, and atherosclerosis. Am J Rhinol Allergy 30:e58–e61, 2016.

9. Frenzo M, Häkkanson K, Schwer S, et al. Asthma in ear, nose, and throat primary care patients with chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy 30:e68–e71, 2016.

10. Li X, Wang X, Lin X, et al. Semi-depot house-dust mite allergen extract for Chinese with allergic rhinitis and asthma. Am J Rhinol Allergy 30:201–208, 2016.

11. Kim DH, Park YS, Jang HJ, et al. Prevalence and allergen of allergic rhinitis in Korean children. Am J Rhinol Allergy 30:e62–e67, 2016.

12. Freitas MS, de Codoba Lanza F, Soares Monteiro JC, and Solé D. Prevalence of rhinitis and associated factors in schoolchildren who live in the Amazon islands. Am J Rhinol Allergy 30:e79–e82, 2016.

13. El-Anwar MW, Nofal AAF, and El-Ahl MA. Electrocauterization and no packing during FESS: A randomized controlled trials. Am J Rhinol Allergy 30:e95–e99, 2016.

14. Lin GC, Freitag SK, Kocharyan A, et al. Comparative techniques of medial rectus muscle retraction for endoscopic exposure of the medial intraconal space. Am J Rhinol Allergy 30:226–229, 2016.

15. Craig JR, Petrov D, Khalili S, et al. The nasofrontal beak: A consistent landmark for superior septectomy during Draf III drill out. Am J Rhinol Allergy 30:230–234, 2016.

16. Kirtsreesakul V, Khuanugkikong T, and Ruttanaphisit T. Does oxymetazoline increase the efficacy of nasal steroids in treating nasal polyposis? Am J Rhinol Allergy 30:195–200, 2016.

17. Liu HT, Lin YC, Kuan YC, et al. Intranasal corticosteroid therapy in the treatment of obstructive sleep apnea: A meta-analysis of randomized controlled trials. Am J Rhinol Allergy 30:215–221, 2016.

18. Koc S, Cayli S, Aksakal C, et al. Protective effects of melatonin and selenium against apoptosis of olfactory sensory neurons: A rat model study. Am J Rhinol Allergy 30:e62–e66, 2016.

19. Kim DK, Rhee CS, and Kim JW. Electrocauterization and no packing may be comparable with nasal packing for postoperative hemorrhage after endoscopic sinus surgery. Am J Rhinol Allergy 30:e91–e94, 2016.

20. Hirunwiwatkul P, Charakom N, Teerapraipruk B, and Jongsuebsit T. The effects of a cold pack on postoperative turbinate and/or septal bleeding and pain. Am J Rhinol Allergy 30:222–225, 2016.

21. Bhatia DDS, Paley T, Ramli R, et al. Two-dimensional assessment of the nasal valve area cannot predict minimum cross-sectional area or airflow resistance. Am J Rhinol Allergy 30:190–194, 2016.

22. Yigider AP, Kayhan FT, Yigit O, et al. Skin diseases of the nose. Am J Rhinol Allergy 30:e83–e90, 2016.