Curr Allergy Asthma Rep (2016) 16: 16
DOI 10.1007/s11882-015-0589-y

RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Risk Factors and Comorbidities in Chronic Rhinosinusitis

Derrick Tint[1] · **Stephanie Kubala**[2] · **Elina Toskala**[1]

Published online: 22 January 2016
© Springer Science+Business Media New York 2016

Abstract Chronic rhinosinusitis (CRS) is a heterogeneous disorder that creates a significant burden on the healthcare system. It is caused by a combination of inflammatory, environmental, and host factors; however, the precise mechanism of how each factor leads to CRS continues to be a source of debate. Previous data regarding this topic is often inconsistent or of lower quality. In this article, we review the recent literature on the risk factors and comorbidities in CRS. Large population-based studies have helped establish smoking as a significant risk factor for CRS. The focus has now shifted towards smoking and its effect on long-term outcomes after endoscopic sinus surgery (ESS). Ciliary dyskinesia, both primary and secondary, can affect both the sinonasal cavity and lower airways simultaneously by decreasing the beat frequency of cilia and inducing mucostasis. The effects of secondary dyskinesia may be reversible and there is some evidence to suggest the use of topical mucolytics in patients with CRS. Allergy and variants of sinonasal anatomy have been hypothesized to increase the risk of developing CRS by inducing chronic inflammation and obstructing the sinus ostia. Nevertheless, emerging data regarding these topics continue to produce inconclusive results. Inflammation of the upper and lower airways can occur simultaneously as seen in patients with asthma and aspirin sensitivity. The connection between these pro-inflammatory disease states has been known for many years. Newer evidence include large population-based studies and studies that correlate objective tests, such as computer tomography scans to pulmonary function tests. However, the treatment of CRS and its effects on obstructive airway disease continues to be a topic of debate. More large prospective studies are needed in order to continue refining our knowledge of the disease processes in CRS.

Keywords Chronic rhinosinusitis · Risk factors · Allergy · Asthma · Comorbidities · Smoking

This article is part of the Topical Collection on *Rhinosinusitis*

✉ Elina Toskala
elina.toskala@temple.edu

[1] Temple Head & Neck Institute, 3440 N. Broad Street, Kresge West 3rd Floor, Philadelphia, PA 19140, USA

[2] Lewis Katz School of Medicine at Temple University, 3500 N. Broad Street, Philadelphia, PA 19140, USA

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disorder that creates a significant burden on the healthcare system. It has been well established that CRS is more than just a chronic infection of the sinonasal cavity. Instead, it appears to be induced by a combination of inflammatory, environmental, and host factors [1]. Despite many years of research, the risk factors that lead to the development of CRS continue to be a topic of debate for many researchers because of either inconclusive or conflicting data. More recently, researchers have attempted to answer questions regarding this topic through improvements in methodology or by systematically reviewing the literature. In this article, we will review the risk factors of CRS and focus on recent advances that have been made in the literature.

Smoking

Cigarette smoke has long been implicated to play a significant role in diseases of the upper airway, including CRS. Many

prior population-based studies from the USA and Europe have shown a likely dose-dependent correlation between the active use of cigarette smoke and the development of self-reported CRS [2]. This finding was once again confirmed in the GA^{2}LEN study, which showed that current smoking, as well as increased pack-years, had higher odds ratio of self-reported CRS [3•]. A more recent survey from Korea of 37,753 people investigated cigarette smoking and various rhinologic diseases and found that each additional year of smoking correlated with a 1.5 % increase in self-reported CRS prevalence [4]. Cigarettes not only have an effect on the development of CRS in smokers, it may also affect those nearby in the form of secondhand smoke. In a recent systematic literature review, a majority of all studies (68.4 %) showed a significant association between rhinosinusitis and secondhand smoke exposure. Even more conclusive, five out of six (83.3 %) studies that used objective measures to diagnose CRS (CT, endoscopy) found the association to be significant [5].

Multiple studies have also analyzed the inflammatory effects of tobacco smoke on the sinonasal mucosa. Cigarette smoke induces a physiologic nasal response, including increased nasal airway resistance, nasal irritation, nasal congestion, and rhinorrhea. Tobacco smoke extract has been demonstrated to have adverse effects on sinonasal epithelial mucociliary clearance, innate immune function, and olfactory mucosal metaplasia [2]. Cigarette smoke exposure impairs cell growth and promotes apoptosis of normal healthy nasal epithelial cells, possibly through the VEGF pathway [6]. Smoking not only affects local mucosa inflammation but also affects the body systemically. Active tobacco smoking has been associated with an increase in markers of systemic inflammation while causing a relative reduction in circulating eosinophils [7•]. Cigarette smoke extracts have also been shown to increase intracellular reactive oxygen species (ROS) production, TLR4 expression, LPS binding, and neutrophil chemotaxis. These effects appear to be mitigated by the addition of the antioxidant and mucolytic agent, carbocysteine [8].

While smoking has been consistently shown to increase the risk of developing CRS in a dose-dependent fashion, the mechanism through which tobacco affects the microbiome in the nose is still unclear. Goldstein-Daruech et al. demonstrated that repetitive tobacco smoke exposure induces biofilm formation in a diverse set of bacteria isolated from the sinonasal cavities of patients with CRS. Cultured in vitro, these isolated bacteria form biofilms in the presence of tobacco smoke and revert to non-biofilm forming phenotypes in the absence of tobacco smoke [9•]. In an additional study, smoking led to substantial changes in the sinus microbiome of both CRS and non-CRS patients [10].

The molecular effects on sinonasal receptors have also been evaluated recently. The tobacco smoke toxin, acrolein, has been found to modulate chloride transport in the sinonasal respiratory epithelium through the cystic fibrosis transmembrane conductance regulator (CFTR), causing physiological alterations similar to those found in patients with cystic fibrosis [11]. The activation of secondary Cl^- transport pathways through calcium-activated Cl^- channels (CaCC) has been postulated as a mechanism to bypass defects in CFTR-mediated transport. Virgin et al. demonstrated that exposure to cigarette smoke condensate also reduced CaCC transport in primary sinonasal epithelial cultures [12].

Studies looking at the effects of smoking on endoscopic sinus surgery (ESS) have been less conclusive [13]. Both smokers and non-smokers continue to maintain a significant improvement in preoperative Sino-Nasal Outcome Test-20 (SNOT-20) scores following ESS at a 10-year follow-up [14••]. In one prospective study, continuing to smoke after endoscopic sinus surgery (ESS) did not alter quality of life (QOL) indexes; however, higher smoking volume was more likely to result in worsening postoperative endoscopic scores at >6 months follow-up [15]. A second study with follow-up of 2–9 years showed that while smoking did not influence preoperative symptoms, it did lead to a significantly higher rate of revision surgery (20 % smokers vs 7 % non-smokers) [16]. In a focused study on postoperative QOL, smokers experienced less improvement following ESS in a dose-dependent fashion [17]. The aggregate of these studies suggests that smoking could have a detrimental effect on the long-term outcomes of ESS.

Allergy

The role of allergy in chronic rhinosinusitis (CRS) has been debated for many years. Researchers have postulated that inflammation and swelling of the nasal mucosa in patients who suffer from allergic rhinitis can obstruct the sinus ostia predisposing them to developing CRS [18]. However, despite having been studied for many years, there is both data to support and dispute that allergy is a significant risk factor for CRS [19–21].

More recently, researchers have attempted to clarify the relationship between CRS and atopy by separating those with nasal polyps (CRSwNP) and those without nasal polyps (CRSsNP). Tan et al. performed a prospective case control series looking at patients with CRSwNP, CRSsNP, and rhinitis and found that the rates of having a positive skin prick test were not statistically different. However, they found that patients with CRS regardless of the presence of polyps had a higher number of sensitivities to different allergies. [22]. Gorgulu et al. looked at patients who underwent endoscopic sinus surgery and also found no relationship between allergy and the development of nasal polyps [23]. In contrast, a recent pilot study looking at patients who relapsed following endoscopic sinus surgery had a significantly increased likelihood of being atopic [24].

Previous studies also looked at skin prick testing for food allergies in patients with CRS and showed rates as high as 70–81 % [25, 26]. Lill et al. did radioallergosorbent (RAST) testing for food allergy in 50 patients with CRSwNP compared to healthy controls. They found that milk allergy alone could be a predisposing factor to CRS; however, they also found rates of food allergy that were much lower than previously reported [27•]. This discrepancy may be due to the use of RAST testing instead of skin testing.

Recent publications looking at the effect of atopy on CRS in the pediatric population are equally confusing. A prospective study looking at children under the age of 13 found that children with chronic and recurrent rhinosinusitis had higher odds (OR 4.2) of being atopic [28]. However, another study looking at a cohort of 117 patients with allergic rhinitis found no association between patients who had aeroallergen sensitivities and the future development of CRS [29].

The relationship between allergy and CRS is still unclear because the literature contains several conflicting studies. A recent systematic review found 10 studies showing an association, 7 studies showing no association, and 1 with a possible association [30]. The evidence regarding this topic has been unable to provide a clear answer regarding the allergy and the role it plays in CRS.

Anatomic Variations

Variations in sinonasal anatomy such as concha bullosa, septal deviation, and deviation of the uncinate process have been postulated to obstruct the ostiomeatal complex (OMC) and thus be a risk factor to the development of CRS. These anatomic variations are particularly important for surgical candidates because they can be addressed at the time of surgery [31]. Previous data looking into this topic did not appear to support these claims [32]; however, recent advances looking at the effect of sinonasal variations and its role in CRS are beginning to suggest that these changes may actually be important.

A prospective study of patients with CRS measured the rates of different anatomic variations on CT and nasal endoscopy and found that 88.2 % of patients had a deviated nasal septum and 76.4 % had concha bullosa [33]. However, while several retrospective and case control trials have shown similarly high rates of anatomical variations, they were unable to conclusively show that these variations were more prevalent in patients with CRS than compared to healthy controls [34, 35]. Therefore, they argued that a variation in sinonasal anatomy was not a risk factor to developing CRS.

Although not increased in prevalence in patients with CRS, different anatomic variations and its effect on disease in specific paranasal sinuses are not as clear. While some studies found no correlation [34], others suggest that certain anatomic changes may have a sinus-specific effect. Vincent and Gendeh looked at patients who underwent FESS and found that patients with concha bullosa did not have an increased likelihood of having a disease in the ipsilateral sinus in comparison to the contralateral one [36]. Another prospective study looked at 67 patients with CRS diagnosed with CT and nasal endoscopy. They found that the increased angle of nasal septal deviation significantly correlated with the increased incidence of maxillary sinus changes [37]. A recent retrospective study of 140 patients with CRS found that septal deviation, concha bullosa, and Haller's cell are correlated with increased maxillary sinus disease while deviation of uncinate process and ethmoid bulla hypertrophy are correlated with increased ethmoid disease.

Although patients with CRS do not necessarily have higher rates of specific anatomic variations, there is mounting evidence to show that these variations, when present, can affect specific paranasal sinuses in individuals with CRS.

Ciliary Dysfunction

Although CRS has multiple etiologies, a unifying manifestation of the disease is mucus hypersecretion with an associated decrease in mucus clearance. Primary (genetic) and secondary (acquired) ciliary dyskinesias are one cause of reduced mucocilliary elimination. Ciliated cells are found in both the upper and lower respiratory tracts, and dysfunction of these cilia can lead to increased rates of infection anywhere along their pathway.

Primary ciliary dyskinesia (PCD) is a rare autosomal-recessive disease with an underlying pathogenesis of disrupted ciliary function, leading to delayed mucus transportation and chronic inflammation. In a survey answered by 44 patients with PCD, other otorhinolaryngologic symptoms, especially chronic otitis media (81 %) and CRS (59 %), were frequently associated with PCD [38]. Many mutations in three genes (DNAI1, DNAH5, DNAH11) encoding for dynein proteins have been implicated as causes of PCD. Most recently, a novel mutation of DNAH5 (c. 8030G > A) was discovered in a Chinese individual who suffered from early onset respiratory infections and persistent CRS [39]. While there are many studies on adult PCD, there is a paucity of evidence on the medical/surgery treatment and outcomes of chronic rhinosinusitis in children with primary ciliary dyskinesia. A recent review has recommended that there should be an international, multicenter database for prospective data collection on the diagnosis, treatment, and outcomes of CRS for children with PCD [40].

Secondary ciliary dyskinesia (SCD) differs from PCD not only on the former's reversibility but also on their ultrastructure. PCD abnormalities most often include defects in the dynein arms (55 %), absence of axonemes (17 %), and ciliary aplasia (14 %), which were found in more than 30 % of cilia

analyzed. SCD abnormalities include peripheral tubular abnormalities and ciliary edema. However, these changes were present in less than 5 % of cilia examined [41].

Secondary ciliary dysfunction in CRS has been found to be the result of multifactorial influences including biochemical, environmental, and mechanical stimuli [42, 43•]. Low ciliary activity and decreased mucociliary clearance has been measured in patients with CRS [44, 45]. Respiratory cilia beat continually at a basal rate. During times of stress such as exercise or infection, ciliary beat frequency (CBF) increases and accelerates the clearance of mucus [46]. Chen et al. examined both basal and stimulated CBF in patients with CRS and control. They found that patients with CRS had no difference in basal CBF, but noted a significant decrease in stimulated CBF [47]. An additional study not only confirmed this blunted response to environmental insults but also found it to revert back to a functional phenotype within 36 hours [48••].

It has been demonstrated that the CRS-associated mucostasis may also be reversible with treatment. In patients with CRS, decreased nasal mucociliary transit time recovered significantly after normal saline nebulization [40]. Surfactant administration has also been postulated to improve mucociliary clearance. Respiratory mucosal explants and air-liquid interface cultures demonstrated robust ciliary beating after the topical application of the novel sinonasal surfactant solution diluted in bicarbonate-buffered saline. Additionally, a 12 to 26 % increase in CBF was recorded after this application [49]. Topical surfactant administration has been shown to be an effective mucolytic treatment for patients with CRS. While effective as mucolytics, these studies have not shown that its application is effective for CRS. Targeting CBF and improving mucus clearance may end the cycle of infection and inflammation and may turn out to be a viable treatment modality for patients with CRS. However, additional studies looking at mucolytics and their effectiveness in CRS need to be performed.

Bronchiectasis

Impairment of ciliary function is also found in patients with bronchiectasis and has been suggested as a comorbid condition with CRS due to their similar pathophysiology. The classic examples are patients with PCD and Kartagener's syndrome who have lifelong difficulty with both CRS and bronchiectasis [50]. The addition of CRS in patients who suffer from bronchiectasis has been shown to decease their sense of smell and have a negatively impact on their quality of life [51, 52]. A retrospective review of patients with radiographic evidence of sinus disease showed that patients with bronchiectasis had worse Lund-Mackay scores than compared with patients with allergic rhinitis. There was also a significant correlation between upper and lower airway bacterial cultures [53]. A prospective study of patients from Spain with idiopathic and post-infective bronchiectasis found that 77 % of these patients had concurrent CRS meeting the EP3OS criteria. Furthermore, patients with CRS had significantly higher bronchiectasis severity scores compared to the patients without CRS [54]. A similar study of the Chinese population also showed patients with concurrent CRS and bronchiectasis had higher bronchiectasis severity scores and poorer forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1), but the results did not reach statistical significance [55]. Recent evidence supports the unified airway theory by showing that the impairment of ciliary function often occurs in both the upper and lower airways simultaneously.

Asthma

The association between respiratory and nasal symptoms has been established for many years. In 1996, the ECRHS study showed a strong relationship between self-reported symptoms of wheezing and nasal allergies [56]. While allergic rhinitis and asthma both share a common etiology involving a hyper reactive inflammatory response to a stimulus, the relationship between asthma and CRS is much more poorly understood. However, there is mounting evidence to show that asthma and CRS are comorbid conditions.

Several studies have been performed recently looking into the relationship of CRS and asthma. In the GA^{2}LEN questionnaire, 52,000 adults were surveyed. Using specific criteria to estimate the prevalence of asthma and CRS based on self-reported symptoms, the survey found that patients with asthma had a higher likelihood of having CRS [57]. Tan et al. provided further evidence in a large retrospective analysis of electronic medical data in the Geisinger system showing that patients recently diagnosed with CRS had a higher likelihood of having preceding diagnosis of asthma [58].

Several studies have also attempted to objectively identify cases of CRS using radiologic data. These studies clearly provide support in the relationship between asthma and CRS. Asthmatic patients who had undergone head imaging have a 47 % prevalence of abnormal sinus roentgenograms, significantly elevated from patients with just rhinitis [59]. Conversely, patients undergoing sinus surgery with more severe mucosal changes on CT were also more likely to report a history of wheezing when compared to those with mild changes [60]. More recently, Lee et al. improved upon these earlier studies by measuring the rates of obstructive lung disease using pulmonary function testing. They once again confirmed this relationship showing that patients with radiologic evidence of sinus disease had significantly decreased lung function [61].

While there is overwhelming evidence to show that rhinosinusitis and asthma are comorbid conditions, there is

also ample evidence supporting a connection between nasal polyposis and bronchial hyper-reactivity in several population-based studies. Patients who report the presence of nasal polyps also have significantly increased likelihood of reporting symptoms of wheezing and asthma [62–64]. Furthermore, the presence of nasal polyps confirmed both radiographically and endoscopically has been correlated with significantly decreased FEV1/FVC ratios in pulmonary function testing. The mechanism for why nasal polyps and obstructive airway disease occur together is still unclear. Several recent articles have examined nasal polyps and bronchial mucosa of asthmatics and found several common inflammatory mediators [65–67].

Researchers are now examining whether the treatment of CRS can lead to improvements in asthma. The treatment of CRS and its effects on the airway are still unclear. Several recent review articles have been conducted looking at the ESS and lung function [68]. Overall, the studies reviewed in this topic are of low quality, and there has only been one study that has used PFTs as an outcome measure for measuring improvements in asthma. Both reviews concluded that there is insufficient evidence supporting ESS in patients with CRS [69–71].

Aspirin Sensitivity

Patients who have aspirin sensitivity are theorized to be more prone to be in an eosinophilic inflammatory state due to a shift in the arachadonic acid pathway. This manifests clinically as nasal polyps in the upper airways and aspirin-exacerbated respiratory disease (AERD) and asthma in the lower airways [72]. Aspirin sensitivity, asthma, and nasal polyps can occur together and is also known as Samter's Triad [73]. Increased inflammation in patients with aspirin sensitivity occurs through both local and systemic mediators [1]. Patients with AERD when challenged with aspirin had longer disease duration, increased number of nasal eosinophils, and elevated levels of serum leukotriene E4. A prospective study of patients undergoing ESS found a high prevalence of AERD (33 %) using the aspirin challenge test and measuring urine leukotriene E4 [74].

Conclusion

The risk factors and comorbidities that are associated with CRS still continue to be a topic of debate due to high heterogeneity in study design with conflicting results and a paucity of high-quality studies. While the quality of evidence remains weak, there is overwhelming data to show that cigarette smoke and ciliary dysfunction increase the risk of developing CRS. The obstruction of the sinus ostia due to the presence of anatomical variants was once thought to be a negligible factor; however, recent advances are beginning to show that they may have an effect. Lastly, there is mounting evidence to support the theory of a unified airway. Ciliary dysfunction and inflammation appear to occur simultaneously in the upper and lower airways as seen in patients who have CRS concurrently with bronchiectasis, asthma, or aspirin sensitivity. Newer evidence using objective measures such as radiographic changes and PFTs has solidified their associations. Emerging data regarding the risk factors and comorbidities of CRS continues to shape our understanding of the complexity of its disease processes.

Compliance with Ethical Standards

Conflict of Interest Drs. Tint, Kubala, and Toskala declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Fokkens, W.J., et al., European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl, 2012(23): p. 3 p preceding table of contents, 1–298.
2. Reh DD, Higgins TS, Smith TL. Impact of tobacco smoke on chronic rhinosinusitis: a review of the literature. Int Forum Allergy Rhinol. 2012;2(5):362–9.
3. • Hastan D et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA(2)LEN study. Allergy. 2011;66(9): 1216–23. **In this European multicentre survey, about one in ten participants had self-reported CRS, and there was an increased odds ratio of CRS in smokers.**
4. Lee WH et al. Effects of cigarette smoking on rhinologic diseases: Korean National Health and Nutrition Examination Survey 2008–2011. Int Forum Allergy Rhinol. 2015;5(10):937–43.
5. Hur K, Liang J, Lin SY. The role of secondhand smoke in sinusitis: a systematic review. Int Forum Allergy Rhinol. 2014;4(1):22–8.
6. Lee HS, Kim J. Cigarette smoke inhibits nasal airway epithelial cell growth and survival. Int Forum Allergy Rhinol. 2013;3(3):188–92.
7. • Berania I et al. Active smoking status in chronic rhinosinusitis is associated with higher serum markers of inflammation and lower serum eosinophilia. Int Forum Allergy Rhinol. 2014;4(5):347–52. **Active smoking not only increases inflammation locally but also systemically, which may be reversible with cessation.**
8. Pace E et al. Oxidative stress and innate immunity responses in cigarette smoke stimulated nasal epithelial cells. Toxicol In Vitro. 2014;28(2):292–9.
9. • Goldstein-Daruech N et al. Tobacco smoke mediated induction of sinonasal microbial biofilms. PLoS One. 2011;6(1):e15700. **There**

is robust biofilm formation when ex vivo bacteria is exposed to tobacco smoke, which revert to a non-biofilm producing phenotype without tobacco smoke.

10. Ramakrishnan VR, Frank DN. Impact of cigarette smoking on the middle meatus microbiome in health and chronic rhinosinusitis. Int Forum Allergy Rhinol. 2015;5(11):981–9.
11. Alexander NS et al. Cystic fibrosis transmembrane conductance regulator modulation by the tobacco smoke toxin acrolein. Laryngoscope. 2012;122(6):1193–7.
12. Virgin FW et al. Exposure to cigarette smoke condensate reduces calcium activated chloride channel transport in primary sinonasal epithelial cultures. Laryngoscope. 2010;120(7):1465–9.
13. Uhliarova B et al. The effect of smoking on CT score, bacterial colonization and distribution of inflammatory cells in the upper airways of patients with chronic rhinosinusitis. Inhal Toxicol. 2014;26(7):419–25.
14.•• White LC et al. The effect of smoking on quality of life following sinus surgery: 10-year follow-up. ORL J Otorhinolaryngol Relat Spec. 2015;77(1):39–43. **No difference in quality of life outcomes was found between smokers and non-smokers 10 years after functional endoscopic sinus surgery.**
15. Rudmik L, Mace JC, Smith TL. Smoking and endoscopic sinus surgery: does smoking volume contribute to clinical outcome. Int Forum Allergy Rhinol. 2011;1(3):145–52.
16. Krzeski A et al. Influence of cigarette smoking on endoscopic sinus surgery long-term outcomes. Rhinology. 2011;49(5):577–82.
17. Katotomichelakis M et al. The effects of smoking on quality of life recovery after surgery for chronic rhinosinusitis. Rhinology. 2014;52(4):341–7.
18. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg. 1997;117(3 Pt 2):S1–7.
19. Jones NS et al. The prevalence of allergic rhinitis and nasal symptoms in Nottingham. Clin Otolaryngol Allied Sci. 1998;23(6):547–54.
20. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy. 1971;29(12):631–4.
21. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. J Allergy Clin Immunol. 1977;59(1):17–21.
22. Tan BK et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. Int Forum Allergy Rhinol. 2011;1(2):88–94.
23. Gorgulu O et al. Analysis of the roles of smoking and allergy in nasal polyposis. Ann Otol Rhinol Laryngol. 2012;121(9):615–9.
24. Yacoub MR et al. Are atopy and eosinophilic bronchial inflammation associated with relapsing forms of chronic rhinosinusitis with nasal polyps? Clin Mol Allergy. 2015;13(1):23.
25. Collins MM et al. Nasal polyposis: prevalence of positive food and inhalant skin tests. Otolaryngol Head Neck Surg. 2006;135(5):680–3.
26. Pang YT, Eskici O, Wilson JA. Nasal polyposis: role of subclinical delayed food hypersensitivity. Otolaryngol Head Neck Surg. 2000;122(2):298–301.
27.• Lill C et al. Milk allergy is frequent in patients with chronic sinusitis and nasal polyposis. Am J Rhinol Allergy. 2011;25(6):e221–4. **In a study of 50 patients with chronic polyposis, 14% were positive for undiagnosed milk allergy by RAST testing compared with none of the tested healthy subjects.**
28. Choi SH et al. Predisposing factors associated with chronic and recurrent rhinosinusitis in childhood. Allergy Asthma Immunol Res. 2012;4(2):80–4.
29. Sedaghat AR, Phipatanakul W, Cunningham MJ. Atopy and the development of chronic rhinosinusitis in children with allergic rhinitis. J Allergy Clin Immunol Pract. 2013;6(1):689–91. **e2**.
30. Wilson KF, McMains KC, Orlandi RR. The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2014;4(2):93–103.
31. Zinreich SJ et al. Concha bullosa: CT evaluation. J Comput Assist Tomogr. 1988;12(5):778–84.
32. Jones NS. CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings. Clin Otolaryngol Allied Sci. 2002;27(1):11–7.
33. Tiwari R, Goyal R. Study of anatomical variations on CT in chronic sinusitis. Indian J Otolaryngol Head Neck Surg. 2015;67(1):18–20.
34. Kaygusuz A et al. Sinonasal anatomical variations: their relationship with chronic rhinosinusitis and effect on the severity of disease-a computerized tomography assisted anatomical and clinical study. Indian J Otolaryngol Head Neck Surg. 2014;66(3):260–6.
35. Azila A et al. The prevalence of anatomical variations in osteomeatal unit in patients with chronic rhinosinusitis. Med J Malaysia. 2011;66(3):191–4.
36. Vincent TE, Gendeh BS. The association of concha bullosa and deviated nasal septum with chronic rhinosinusitis in functional endoscopic sinus surgery patients. Med J Malaysia. 2010;65(2):108–11.
37. Poorey VK, Gupta N. Endoscopic and computed tomographic evaluation of influence of nasal septal deviation on lateral wall of nose and its relation to sinus diseases. Indian J Otolaryngol Head Neck Surg. 2014;66(3):330–5.
38. Sommer JU et al. ENT manifestations in patients with primary ciliary dyskinesia: prevalence and significance of otorhinolaryngologic co-morbidities. Eur Arch Otorhinolaryngol. 2011;268(3):383–8.
39. Zhang J et al. A novel mutation of DNAH5 in chronic rhinosinusitis and primary ciliary dyskinesia in a Chinese family. Eur Arch Otorhinolaryngol. 2014;271(6):1589–94.
40. Mener DJ et al. Treatment and outcomes of chronic rhinosinusitis in children with primary ciliary dyskinesia: where is the evidence? A qualitative systematic review. Int Forum Allergy Rhinol. 2013;3(12):986–91.
41. Demarco RC et al. Ciliary ultrastructure in patients with chronic rhinosinusitis and primary ciliary dyskinesia. Eur Arch Otorhinolaryngol. 2013;270(7):2065–70.
42. Joki S et al. Correlation between ciliary beat frequency and the structure of ciliated epithelia in pathologic human nasal mucosa. Laryngoscope. 1998;108(3):426–30.
43.• Gudis D, Zhao KQ, Cohen NA. Acquired cilia dysfunction in chronic rhinosinusitis. Am J Rhinol Allergy. 2012;26(1):1–6. **Up to date review article on the recent developments in the understanding of cilia dysfunction and mucociliary clearance in CRS**.
44. Al-Rawi MM, Edelstein DR, Erlandson RA. Changes in nasal epithelium in patients with severe chronic sinusitis: a clinicopathologic and electron microscopic study. Laryngoscope. 1998;108(12):1816–23.
45. Nuutinen J et al. Ciliary beating frequency in chronic sinusitis. Arch Otolaryngol Head Neck Surg. 1993;119(6):645–7.
46. Ferguson JL et al. The effects of sinus bacteria on human ciliated nasal epithelium in vitro. Otolaryngol Head Neck Surg. 1988;98(4):299–304.
47. Chen B et al. Altered sinonasal ciliary dynamics in chronic rhinosinusitis. Am J Rhinol. 2006;20(3):325–9.
48.•• Chen B et al. Reversal of chronic rhinosinusitis-associated sinonasal ciliary dysfunction. Am J Rhinol. 2007;21(3):346–53. **Sinonasal mucosal explants from CRS patients show blunted responses to the environment which reverses to a stimulatory phenotype within 36 h of culturing.**
49. Chiu AG et al. Safety evaluation of sinus surfactant solution on respiratory cilia function. Int Forum Allergy Rhinol. 2011;1(4):280–3.
50. Philpott CM, McKiernan DC. Bronchiectasis and sino-nasal disease: a review. J Laryngol Otol. 2008;122(1):11–5.

51. Guilemany JM et al. United airways: the impact of chronic rhinosinusitis and nasal polyps in bronchiectasic patient's quality of life. Allergy. 2009;64(10):1524–9.
52. Guilemany JM et al. The importance of smell in patients with bronchiectasis. Respir Med. 2011;105(1):44–9.
53. Ramakrishnan VR et al. Upper and lower airways associations in patients with chronic rhinosinusitis and bronchiectasis. Int Forum Allergy Rhinol. 2013;3(11):921–7.
54. Guilemany JM et al. United airways again: high prevalence of rhinosinusitis and nasal polyps in bronchiectasis. Allergy. 2009;64(5):790–7.
55. Guan WJ et al. Impacts of co-existing chronic rhinosinusitis on disease severity and risks of exacerbations in Chinese adults with bronchiectasis. PLoS One. 2015;10(9):e0137348.
56. Burney P et al. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J, 1996. **9**(4): 687–95.
57. Jarvis D et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67(1):91–8.
58. Tan BK et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2013;131(5):1350–60.
59. Schwartz HJ et al. Occult sinus abnormalities in the asthmatic patient. Arch Intern Med. 1987;147(12):2194–6.
60. Newman LJ et al. Chronic sinusitis. Relationship of computed tomographic findings to allergy, asthma, and eosinophilia. JAMA. 1994;271(5):363–7.
61. Lee SY et al. Influence of chronic sinusitis and nasal polyp on the lower airway of subjects without lower airway diseases. Allergy Asthma Immunol Res. 2014;6(4):310–5.
62. Klossek JM et al. Prevalence of nasal polyposis in France: a cross-sectional, case-control study. Allergy. 2005;60(2):233–7.
63. Hedman J et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol. 1999;28(4):717–22.
64. Johansson L et al. Prevalence of nasal polyps in adults: the Skovde population-based study. Ann Otol Rhinol Laryngol. 2003;112(7): 625–9.
65. Hakansson K et al. Airway inflammation in chronic rhinosinusitis with nasal polyps and asthma: the united airways concept further supported. PLoS One. 2015;10(7):e0127228.
66. Machado-Carvalho L, Roca-Ferrer J, Picado C. Prostaglandin E2 receptors in asthma and in chronic rhinosinusitis/nasal polyps with and without aspirin hypersensitivity. Respir Res. 2014;15:100.
67. Frieri M. Asthma linked with rhinosinusitis: an extensive review. Allergy Rhinol (Providence). 2014;5(1):41–9.
68. Lehrer E et al. Management of chronic rhinosinusitis in asthma patients: is there still a debate? Curr Allergy Asthma Rep. 2014;14(6):440.
69. de Bruin, R.J., et al., Rapid review: sinonasal surgery vs. medical therapy for asthma in patients with chronic rhinosinusitis with or without nasal polyps. Eur Arch Otorhinolaryngol, 2015.
70. Rix I et al. Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: a systematic review. Am J Rhinol Allergy. 2015;29(3):193–201.
71. Vashishta R et al. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. Int Forum Allergy Rhinol. 2013;3(10):788–94.
72. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease: update on pathogenesis and desensitization. Semin Respir Crit Care Med. 2012;33(6):588–94.
73. Samter M, Beers Jr RF. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. Ann Intern Med. 1968;68(5): 975–83.
74. Celejewska-Wojcik N et al. Incidence of aspirin hypersensitivity in patients with chronic rhinosinusitis and diagnostic value of urinary leukotriene E4. Pol Arch Med Wewn. 2012;122(9):422–7.