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REVIEW

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Progression from nasal polyps to adult-onset asthma: a different process from atopic march?*

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Abstract

Nasal polyps and comorbid asthma (NPcA) is a severe clinical entity, which is often treated as a united airway disease. Asthma is frequently associated with allergic rhinitis and nasal polyps and the natural course of asthma has long been explored. The "atopic march" has been proposed for decades to explain the progression of the united airway diseases. The atopic march principally relates to the development of childhood asthma from atopic conditions. In contrast, adult-onset asthma, which is often non-atopic and more severe, has been shown to be highly associated with nasal polyps. Recently, asthma onset pattern and its association with upper airway diseases have gained increasing attention, which is partly due to the different phenotypes of asthma with respect to comorbidity, disease severity, and treatment responses. Despite extensive research over the past years, the progression of asthma from upper airway diseases remain incompletely defined. This review compares the natural course of childhood and adult-onset asthma and highlights the distinct progression of NPcA. Additionally, risk factors, mechanisms and potential targets of NPcA are also summarized. Advancements in understanding the natural course and pathogenic mechanisms of NPcA may guide the effective therapeutic strategies or possibly curb the progression of NPcA.

Key words: nasal polyps, adult-onset asthma, childhood asthma, natural course, risk factor

Introduction

Nasal polyps and comorbid asthma (NPcA) is a severe upper and lower airway disease characterized by high nasal polyp recurrence rates and corticosteroid dependence [1,2]. There is growing evidence that supports the disease entity of NPcA from the perspective of the prevalence, phenotype and disease course [3-6]. Indeed, approximately 20% to 60% of patients with nasal polyps have asthma [7-9] and approximately 7% to 25.4% of patients with asthma have nasal polyps [10]. What's more, about 19.30% to 38.64% patients with adult-onset asthma have nasal polyps [11-13]. This indicates a high association between adult-onset asthma and nasal polyps.

Recent studies show that the comorbidity of nasal polyps significantly influences the remission and persistence of adult-onset asthma [13], characterizes by severe or difficult-to-treat asthma [14,15], and highly associates with increased asthma hospitalization [16]. Similarly, chronic rhinosinusitis (CRS) patients with late-onset asthma have more frequent nasal polyps and late-onset asthma might be a predictor of more severe disease in CRS [17]. Furthermore, a study by Lin et al. showed that increasing severity of asthma was associated with a greater prevalence of nasal polyps and radiological severity of CRS [18]. While multiple studies have explored the association between CRS and asthma, there is not enough information about the natural course of NPcA. It is imperative to explore the natural course, risk factors, and mechanism of NPcA. This review describes the differences in the natural history of childhood asthma and adult-onset asthma and highlights the distinct progression of NPcA. Advances in the pathogenesis of the NPcA are also summarized.

Different roles for the atopic march in the progression of childhood versus adult-onset asthma

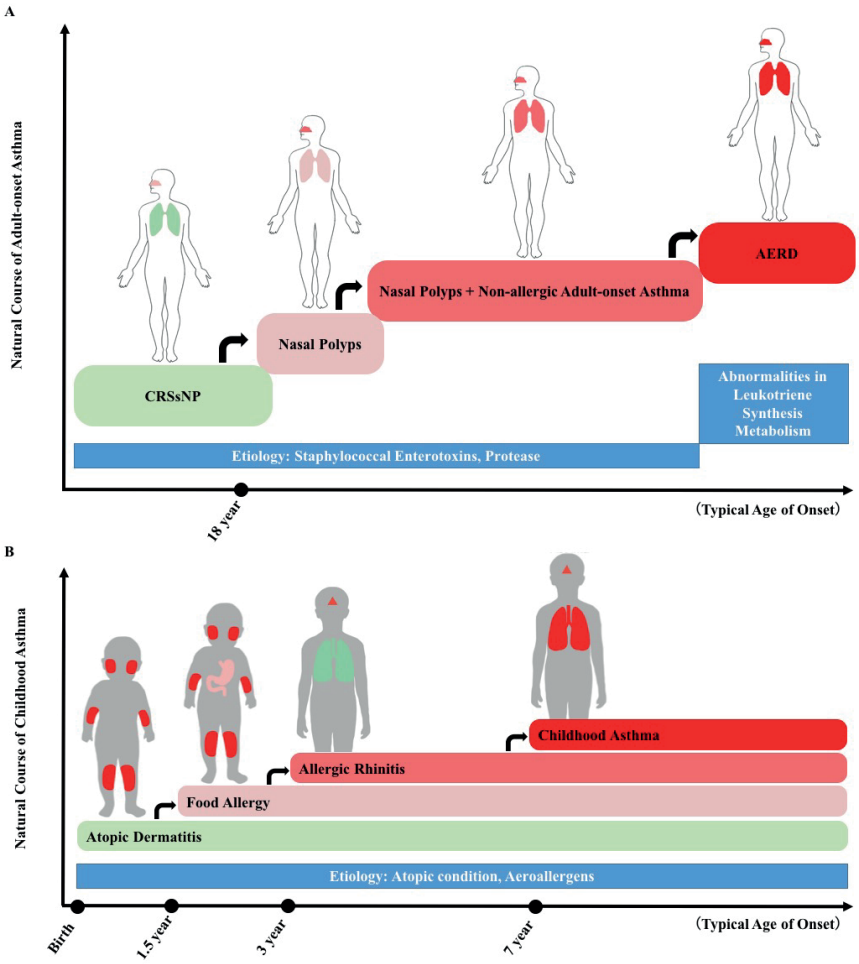

Figure 1. A hypothetical diagram for two different marches of united airway diseases. (A) The natural course of non-allergic adult-onset asthma which starts from chronic rhinosinusitis without nasal polyps. Etiology factors include Staphylococcus aureus, proteases, and abnormalities in leukotriene synthesis metabolism. (B) The natural course of childhood asthma which involved in the atopic march. Etiology factors include atopic condition and aeroallergens.

The concept of the atopic march (Figure 1) has been well acknowledged and a series of risk factors for the development of childhood asthma have been identified including atopic dermatitis, frequent wheezing during the first years, allergic rhinitis, peripheral blood eosinophilia of 4% or greater, and allergic sensitization to aeroallergens [19-21]. Childhood asthma is typically associated with other atopic conditions, such as allergic rhinitis and atopic dermatitis and the amounts of total and specific IgE are higher in childhood asthma than in adult-onset asthma [22,23]. Epidemiological data show that up to 80% of patients with asthma suffer from allergic rhinitis [24] and approximately 15% to 38% of patients with allergic rhinitis have asthma [25]. Furthermore, allergic rhinitis often precedes asthma [26,27]. Recently, a study by Tran et al. showed it is a combination of atopic dermatitis and allergic sensitization, not atopic dermatitis alone, is associated with an increased risk of asthma at age 3 [28]. Thus, the development of childhood asthma is highly associated with allergy [22]. In contrast, adult-onset asthma is often non-atopic [29,30], especially in severe adult-onset asthma [12]. A 14-year longitudinal study which aimed to identify risk factors of adult-onset asthma concluded that neither pre-existing atopy nor new atopy was associated with adult-onset asthma [31]. A recent study shows that atopy is negatively correlated with age of asthma onset in elderly patients [32]. Additionally, a longitudinal study concluded that the development of adult-onset asthma in rhinitis is independent of allergy [33]. Furthermore, adult-onset asthma is often associated with specific triggers such as occupational agents [34], aspirin intake [35], cigarette smoke [31], and respiratory tract infection [36]. However, there was also opposite evidence that atopic symptoms and the family history of atopy were associated with the incidence of adult-onset asthma [37]. It seems that the progression of adult-onset asthma does not fit well with the principle of atopic march or allergic united airway disease [38-40] and may represent a unique subtype of diseases entitled non-allergic united airway diseases.

From allergic airway diseases to non-allergic airway diseases: focus on the severity

The link between upper and lower airways has long been studied for about two decades since the proposition of united airway disease [41] with a main focus on the allergic rhinitis and asthma [42-44]. When atopic march firstly progresses into the upper airway [45,46], the rest of the march is commonly discussed in allergic united airway disease [38,40,47], which is mainly linked to the progression of childhood asthma from allergic rhinitis [48-50]. The concept of atopic march can explain the progression of allergic united airway diseases, but it does not apply to the non-allergic united airway diseases, for example, adult-onset asthma with nasal polyps. Furthermore, the risk factors, development, and prognosis of adult-onset are proved to be different from childhood asthma [29-31,51].

Although comorbidity of allergy or atopy significantly influences the airway disease course, it seems that inhaled allergens are fewer contributors to the pathogenesis and disease severity of adult-onset asthma [11,12,29]. Our understanding of united airway disease has expanded and non-allergic airway disease (e.g. adult-onset asthma and nasal polyps) has gained more attention for its more severity [1,12,52]. A new concept about the progression of adult-onset asthma should therefore be proposed.

Role of chronic rhinosinusitis in the development of adult-onset asthma

There are large amounts of evidence that support the high association between CRS and asthma with respect to prevalence [53-56] and disease severity [13,18,57-59], but the exact role of CRS in the development of adult-onset asthma are not well validated. A recent study by Hirsch et al. shows that chronic rhinosinusitis without nasal polyps (CRSsNP) is a significant risk factor for the comorbidity of asthma in the future 5 years [60]. Similarly, a population-based longitudinal study concluded that about one in 13 individuals with CRS would be subsequently diagnosed with adult-onset asthma during the subsequent 12 years [61]. In addition, a population-based epidemiological survey showed that CRS in the absence of nasal allergies was positively associated with late-onset asthma (onset age of asthma ≥ 16 years) and negatively associated with childhood asthma [3], which further supports the unique role of CRS without atopy in the progression of adult-onset asthma. Furthermore, the risk of adult-onset asthma was higher in non-atopic patients with rhinitis than atopic counterparts [62]. In addition, there are also other risk factors for adult-onset asthma such as smoking, snoring, airway hyperresponsiveness [63] and concomitant atopic manifestations, and female [64-67]. It can be inferred that CRS without atopy is a significant risk factor for the progression of adult-onset asthma.

Development of nasal polyps and comorbid asthma: epidemiology and disease course

Clinically, CRS can be divided into chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) [68]. It has been proposed that all types of CRS have the potential to develop NPs when given enough time and insult[69] and CRSwNP is a result of more prolonged and severe inflammation[70,71]. The mean age of NPs onset is 42 years and the typical age of diagnosis ranging from 40 to 60 years [68,72]. From the perspective of the natural course, nasal polyps and comorbid asthma might be an end product of CRS [73] and possibly the most severe type of the united airway diseases [74].

Similar to the development of childhood asthma from allergic rhinitis, nasal polyps and asthma do not occur simultaneously. During the natural evolution of this disease entity, a clinical history of nasal polyps usually precedes asthma, and up to 45% patients with NPs will develop adult-onset asthma [3,75]. Indeed, more than 60% of undiagnosed asthmatic patients with NPs have some level of lower airway involvement [76,77], especially in patients with eosinophilic subtypes of nasal polyps [78,79]. After evaluation of bronchial hyperresponsiveness (BHR) in adult patients with NPs, approximately 28% to 40% patients with NPs had newly diagnosed asthma [77,80-83], indicating that asthma might coexist as a subclinical disease in NPs.

Patients with aspirin exacerbated respiratory disease (AERD) is a distinct phenotype of NPcA, which is usually defined as Samter's triad or nonsteroidal anti-inflammatory drug exacerbated respiratory disease [84,85]. Three cardinal features of AERD include CRSwNP, asthma, and hypersensitivity to cyclooxygenase-1 (COX-1) inhibitors. The underlying pathogenic mechanism appears to be related to abnormalities in leukotriene synthesis metabolism and eosinophil levels [86] and excessive amounts of Cysteinyl leukotrienes is generated with a reflection of urinary leukotriene E4 concentrations [87]. In general, AERD develops quite suddenly in adulthood and the mean age of NPs onset in patients with AERD is 34 years [88]. The clinical course of patients with AERD differs greatly to NPcA patients without sensitive to COX-1 inhibitors [1]. It has been proposed that AERD might be the end stage of the march: from CRS, NPs, adult-onset asthma, and finally AERD [73]. This is based on the cross-sectional studies which show that the risk of future of AERD is high in patients with eosinophilic NPs and comorbid asthma [89,90]. Future longitudinal studies are needed to verify this speculation.

Aspirin desensitization provides therapeutic benefits to patients with nasal polyps in AERD [91-93] and plasma 15-Hydroxyeicosatetraenoic acid is identified as a predictor of the outcome [94]. What's more, the causes of AERD are yet to be determined, and the contributions of potential epigenetic or environmental factors to disease pathogenesis are largely unknown [95]. Therefore, further research is needed to explore the mechanism of AERD and the potential targets for prevention of the AERD.

Risk factors for nasal polyps and comorbid asthma

There is a wide consensus that allergen immunotherapy is the only treatment that alters the course of allergic diseases by preventing the development of asthma and has a long-term efficacy after termination of the treatment [96,97]. However, the pathogenesis of adult-onset asthma is different from childhood asthma. Although several previous studies showed the benefit of endoscopic sinus surgery for the control of asthma in patients with NPcA [2, 98,99], whether early surgery for NPs is an effective treatment to prevent the progression of adult-onset asthma needs further studies. Now, it still lacks a strategy to prevent the progression of adult-onset asthma. Identification of risk factors that promote the formation of NPcA may provide a foundation from which to understand the pathogenesis of NPcA and ultimately to develop primary prevention intervention strategies.

It was shown that NPcA was a unique phenotype different from NPs or asthma [1,5]. A series of risk factors, such as asymptomatic BHR, IL-9, IL-5, *Staphylococcus aureus* enterotoxin (SE)-specific IgE, atopy, sex, allergic rhinitis, and aspirin sensitivity exert different influences on the formation and natural courses of NPcA [82,82,100,101]. A recent study reported a certain endotype of patients with NPcA characterized by the presence of SE-specific IgE and high levels of IL-5 and IgE [5]. Our recent study based on cluster analysis of disease history shows that patients with NPcA exhibit three clinical phenotypes with distinct natural courses [102]. Furthermore, the disease duration, the age of nasal symptoms onset, age at subsequent asthma diagnosis, and history of family asthma are different among three clusters, which possibly points out the heterogeneity among patients with NPcA.

Mechanism of nasal polyps and comorbid asthma and potential targets

Previous studies showed that total IgE was a biomarker for eosinophilic NPcA [6] and a human anti-IgE mAb demonstrated clinical efficacy in the treatment of NPcA, which supported the functionality of local IgE formation in the airways of patients with NPcA [103,104]. Additionally, the presence of IL-5 proteins and IgE antibodies to staphylococcal enterotoxins in NPs was associated with comorbid asthma suggesting a causal role of staphylococcal enterotoxins in chronic upper and lower airways disease. It has been shown that staphylococcal enterotoxins played a crucial role in the pathogenesis of adult-onset asthma [105-107]. Furthermore, *Staphylococcus aureus*, the local superantigens in the airway, was treated as a strong link between upper and lower airway diseases and asthma comorbidity could be the consequence of local superantigen-induced inflammation in nasal cavity [108-110]. However, whether intervention targeting *Staphylococcus aureus* in the early stage of NPcA patients is an effective way to prevent the progression of adult-onset asthma is still unknown.

Periostin has been proposed as a biomarker for the Th2-skewed immune responses in asthmatic patients [111]. Periostin is an extracellular matrix and a matricellular protein facilitating tissue remodeling and it is produced primarily by fibroblasts in response to IL-4 and IL-13 [112,113]. Elevated serum levels of periostin are highly associated with asthma exacerbations [114,115] and the presence of late-onset eosinophilic asthma [116]. Furthermore, serum periostin has been identified as a biomarker for comorbid nasal polyps in patients with asthma [117,118]. There is also more and more evidence supporting the role of periostin in patients with AERD. Recent studies suggest that periostin levels are elevated in tissues from patients with CRSwNP compared with CRSsNP and controls, especially in those with aspirin sensitivity [119,120]. In addition, serum periostin levels are significantly elevated in AERD patients [115], especially in those with severe chronic rhinosinusitis [121]. It can be inferred that periostin plays a crucial role in the pathogenesis of NPcA patients with or without aspirin sensitivity. A recent study by Brook et al. showed that inhibition of periostin expression in patients with NPcA significantly delayed the time to revision sinus surgery by >2 years [122]. Based on these findings, great attention has been paid to periostin as a biomarker or a target to develop therapeutic agents against eosinophilic inflammation in patients with NPcA [123].

The mechanism of Th2-type inflammation in CRSwNP or asthma has recently been advanced [124,125]. The understanding of mechanisms underlying eosinophilic airway diseases has changed from a paradigm in which allergen-driven Th2 lymphocytes are the primary drivers to one in which production of cytokines by a deregulated epithelium is the primary driver for eosinophilic inflammation [126,127]. A large series of both environmental and endogenous stimuli can activate the epithelial cell and elicit the release of pro-Th2 cell chemokines and cytokines [124]. Protease activity is a common feature of many insults [128-130]. External stimuli such as the allergen, fungus, *Staphylococcus aureus* and microbiome disturbance have proved to be significant contributing factors both in asthma [105,131] and CRSwNP [132,133] pathophysiology. Furthermore, epithelial barrier dysfunction caused by external stimuli has been implicated in driving Th2-biased airway [124,134]. Proteases play an important role in initiating and maintaining of eosinophilic airway inflammation [135] and an imbalance between proteases and endogenous protease inhibitors was treated as a crucial contributor in the mechanism of eosinophilic airway diseases [136]. The role of protease activation of inflammation has long been recognized and discussed in allergic respiratory diseases [137]. However, it is not clear whether airway proteases are potential targets in controlling the systematic inflammation of patients with NPcA.

Conclusions and future directions

Both childhood asthma and adult-onset asthma have distinct natural courses and the non-atopic factors are often involved in

the progression of adult-onset asthma. United airway diseases can be divided into allergic and non-allergic united airway subtypes which represent two different marches and development directions. The final stage of the non-allergic united airway diseases is often a more severe disease entity such as NPcA and AERD. Furthermore, the development of adult-onset asthma is highly associated with CRS, especially nasal polyps. Risk factors, such as asymptomatic BHR, IL-9, IL-5, *Staphylococcus aureus* enterotoxin (SE)-specific IgE, atopy, sex, allergic rhinitis, and aspirin sensitivity contribute to the formation of NPcA. Chronic local stimuli mainly from microbiome, such as *Staphylococcus aureus* proteases and their products may be critical in promoting the progression of non-allergic airway diseases. The primary prevention to inhibit NPcA or AERD development should focus on the local microbiome. Longitudinal epidemiological cohort studies are needed to verify these two marches and further preventive measures might be designed to curb the development of marches.

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Authorship contribution

DW drafted the manuscript. BSB and YW revised the manuscript. All authors read and approved the final article.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Stevens WW, Peters AT, Hirsch AG, et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract. 2017 Aug;5(4):1061-1070. e3.
2. Batra PS, Kern RC, Tripathi A, et al. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. Laryngoscope. 2003 Oct;113(10):1703-1706.
3. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012 Jan;67(1):91-98.
4. Bachert C, Zhang N, Holtappels G, et al. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. J Allergy Clin Immunol. 2010 Nov;126(5):962-968. e6.
5. 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 May;137(5):1449-1456. e4.
6. Wu D, Li L, Zhang M, et al. Two inflammatory phenotypes of nasal polyps and comorbid asthma. Ann Allergy Asthma Immunol. 2017 May;118(3):318-325.
7. Promsopa C, Kansara S, Citardi MJ, et al. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. Int Forum Allergy Rhinol. 2016 Apr;6(4):373-377.
8. Klossek J, Neukirch F, Pribil C, et al. Prevalence of nasal polyposis in France: a cross-sectional, case–control study. Allergy. 2005 Feb;60(2):233-237.
9. 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 Nov;122(5):961-968.
10. Ahmadiafshar A, Farjd H, Moezzi F, et al. Nasal polyposis in patients with asthma and allergic rhinitis. J Laryngol Otol. 2012 Aug;126(8):780-783.
11. de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. ERJ Open Res. 2016 May;2(2):00100-2015.
12. Amelink M, de Groot JC, de Nijs SB, et al. Severe adult-onset asthma: a distinct phenotype. J Allergy Clin Immunol. 2013 Aug;132(2):336-341.
13. Westerhof GA, Coumou H, de Nijs SB, et al. Clinical predictors of remission and persistence of adult-onset asthma. J Allergy Clin Immunol. 2018 Jan; 14(1):104-109. e3.
14. Chipps BE, Haselkorn T, Paknis B, et al. More than a decade follow-up in patients with severe or difficult-to-treat asthma: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II. J Allergy Clin Immunol. 2017 Aug 7. http://doi.org/10.1016/j.jaci.2017.07.014.
15. Wu W, Bleecker E, Moore W, et al. Unsupervised phenotyping of Severe Asthma Research Program participants using expanded lung data. J Allergy Clin Immunol. 2014 May;133(5):1280-8.
16. Mahdavinia M, Benhammuda M, Codispoti CD, et al. African American patients with chronic rhinosinusitis have a distinct phenotype of polyposis associated with increased asthma hospitalization. J Allergy Clin Immunol Pract. 2016 Aug;4(4):658-664. e1.
17. Jones C, Price CP, Weibman AR, et al. Asthma onset pattern and patient outcomes in a chronic rhinosinusitis population. Int Forum Allergy Rhinol. 2018 Jan 5. doi: 10.1002/alr.22064.
18. Lin DC, Chandra RK, Tan BK, et al. Association between severity of asthma and degree of chronic rhinosinusitis. Am J Rhinol Allergy. 2011Aug;25(4):205-208.
19. Panettieri RA, Covar R, Grant E, et al. Natural history of asthma: Persistence versus progression—does the beginning predict the end? J Allergy Clin Immunol. 2008 Mar;121(3):607-613.
20. Castro-Rodríguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med. 2000 Oct;162(4):1403-1406.
21. Spergel JM. From atopic dermatitis to asthma: the atopic march. Ann Allergy Asthma Immunol. 2010 Aug;105(2):99-106.
22. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. J Allergy Clin Immunol. 2010 Dec;126(6):1170-1175. e2.
23. Miranda C, Busacker A, Balzar S, Trudeau J and Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol. 2004 Jan;113(1):101-108.
24. Marseglia G, Merli P, Caimmi D, et al. Nasal disease and asthma. Int J Immunopathol Pharmacol. 2011 Oct;24(4):7-12.
25. Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. J Allergy Clin Immunol. 2017 Oct;140(4):950-958.
26. Licari A, Brambilla I, De Filippo M, et al. The role of upper airway pathology as a co-morbidity in severe asthma. Expert Rev Respir

Med. 2017 Nov;11(11):855-865.
27. Zheng T, Yu J, Oh MH, et al. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. Allergy Asthma Immunol Res. 2011 Apr;3(2):67-73.
28. Tran MM, Lefebvre DL, Dharma C, et al. Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study. J Allergy Clin Immunol. 2018 Feb; 141(2): 601-607. e8.
29. Amelink M, Nijs S, Groot J, et al. Three phenotypes of adult-onset asthma. Allergy. 2013;68(5):674-680.
30. de Nijs SB, Venekamp LN and Bel EH. Adult-onset asthma: is it really different? Eur Respir Rev. 2013Mar 1;22(127):44-52.
31. Jamrozik E, Knuiman MW, James A, et al. Risk factors for adult-onset asthma: a 14-year longitudinal study. Respirology. 2009 Aug;14(6):814-821.
32. Agondi RC, Andrade MC, Takejima P, et al. Atopy Is Associated with Age at Asthma Onset in Elderly Patients. J Allergy Clin Immunol Pract. 2017 Nov 23. pii: S2213-2198(17)30874-7.
33. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet. 2008 Sep 20;372(9643):1049-1057.
34. Kogevinas M, Antó JM, Sunyer J, et al. Occupational asthma in Europe and other industrialised areas: a population-based study. Lancet. 1999 May 22;353(9166):1750-1754.
35. Szczeklik A and Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. J Allergy Clin Immunol. 2003 May;111(5):913-921.
36. Dahlberg P and Busse W. Is intrinsic asthma synonymous with infection? Clin Exp Allergy. 2009 Sep;39(9):1324-1329.
37. Toren K and Hermansson B-A. Incidence rate of adult-onset asthma in relation to age, sex, atopy and smoking: a Swedish population-based study of 15813 adults. Int J Tuberc Lung Dis. 1999 Mar;3(3):192-7.
38. Feng CH, Miller MD and Simon RA. The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis. Am J Rhinol Allergy. 2012 Jun;26(3):187-190.
39. Braunstahl G-J. United airways concept: what does it teach us about systemic inflammation in airways disease? Proc Am Thorac Soc. 2009 Dec;6(8):652-654.
40. Passalacqua G, Ciprandi G and Canonica GW. The nose-lung interaction in allergic rhinitis and asthma: united airways disease. Curr Opin Allergy Clin Immunol. 2001 Feb;1(1):7-13.
41. Grossman J. One airway, one disease. Chest. 1997 Feb;111(2):11S-16S.
42. Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004 Jan;113(1):86-93.
43. Demoly P and Bousquet J. The relation between asthma and allergic rhinitis. Lancet. 2006 Aug;368(9537):711-713.
44. Bellanti JA and Settipane RA. United airway disease. Allergy Asthma Proc. 2014 Oct;35(5):355.
45. Hon KLE, Wang SS and Leung T-f. The atopic march: from skin to the airways. Iran J Allergy Asthma Immunol. 2012 Mar;11(1):73-77.
46. Spergel JM. Atopic march: link to upper airways. Curr Opin Allergy Clin Immunol. 2005 Feb;5(1):17-21.
47. Giavina-Bianchi P, Aun MV, Takejima P, et al. United airway disease: current perspectives. J Asthma Allergy. 2016 May 11;9:93-100.
48. Tsilochristou OA, Douladiris N, et al. Pediatric allergic rhinitis and asthma: can the march be halted? Paediatr Drugs. 2013 Dec;15(6):431-440.
49. Compalati E, Ridolo E, Passalacqua G, et al. The link between allergic rhinitis and asthma: the united airways disease. Expert Rev Clin Immunol. 2010 May;6(3):413-423.
50. Bourdin A, Gras D, Vachier I, et al. Upper airway· 1: Allergic rhinitis and asthma: united disease through epithelial cells. Thorax. 2009 Nov;64(11):999-1004.
51. de Marco R, Locatelli F, Cerveri I, et al. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. J Allergy Clin Immunol. 2002 Aug;110(2):228-235.
52. Fokkens WJ and Hellings PW. Nasal polyposis and asthma: the otorhinolaryngologist's view. The Nose and Sinuses in Respiratory Disorders (ERS Monograph) Sheffield, European Respiratory Society. 2017.p. 87-104.
53. Chen YT, Chien CY, Tai SY , et al. Asthma associated with chronic rhinosinusitis: a population-based study. Int Forum Allergy Rhinol. 2016 Dec;6(12):1284-1293.
54. Pakdaman MN and Luong A. The links between chronic rhinosinusitis and asthma. Curr Opin Otolaryngol Head Neck Surg. 2011 Jun;19(3):218-223.
55. Huang C-C, Wang C-H, Fu C-H, et al. The link between chronic rhinosinusitis and asthma: a questionnaire-based study. Medicine. 2016 Aug;95(31):e4295.
56. Shi J, Fu Q, Zhang H, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. Allergy. 2015 May;70(5):533-539.
57. Ek A, Middelveld R, Bertilsson H, et al. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA2LEN survey. Allergy. 2013 Oct;68(10):1314-1321.
58. Banoub RG, Phillips KM, Hoehle LP, et al. Relationship between chronic rhinosinusitis exacerbation frequency and asthma control. Laryngoscope. 2017 Sep 30. http://doi.org/ 10.1002/lary.26901.
59. Phillips KM, Hoehle LP, Bergmark RW, et al. Chronic rhinosinusitis severity is associated with need for asthma-related systemic corticosteroids. Rhinology. 2017 Sep1;55(3):211-217.
60. Hirsch A, Yan X, Sundaresan A, et al. Five-year risk of incident disease following a diagnosis of chronic rhinosinusitis. Allergy. 2015 Dec;70(12):1613-21.
61. Habib ARR, Javer AR and Buxton JA. A population-based study investigating chronic rhinosinusitis and the incidence of asthma. Laryngoscope. 2016 Jun;126(6):1296-1302.
62. Toren K, Olin A-C, Hellgren J, et al. Rhinitis increase the risk for adult-onset asthma—a Swedish population-based case-control study (MAP-study). Respir Med. 2002 Aug;96(8):635-41.
63. Fahrenholz JM. Natural history and clinical features of aspirin-exacerbated respiratory disease. Clin Rev Allergy Immunol. 2003 Apr;24(2):113-24.
64. Jamrozik E, Knuiman M, James A, et al. Risk factors for adult-onset asthma: a 14-year longitudinal study. Respirology. 2009 Aug;14(6):814-21.
65. Porsbjerg C, von Linstow M-L, Ulrik CS, et al. Risk factors for onset of asthma: a 12-year prospective follow-up study. Chest. 2006 Feb;129(2):309-316.
66. Brutsche MH, Downs SH, Schindler C, et al. Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA cohort study. Thorax. 2006 Aug;61(8):671-677.
67. Lundbäck B, Rönmark E, Jönsson E, et al. Incidence of physician-diagnosed asthma in adults--a real incidence or a result of increased awareness? Report from The Obstructive Lung Disease in Northern Sweden Studies. Respir Med. 2001Aug;95(8):685-92.
68. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012 May;50(1):1-12.
69. DeMarcantonio MA and Han JK. Nasal polyps: pathogenesis and treatment implications. Otolaryngol Clin North Am. 2011 Jun;44(3):685-695.
70. Payne SC, Early SB, Huyett P, et al. Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. Laryngoscope. 2011 Oct;121(10):2262-2267.
71. Payne SC, Borish L and Steinke JW. Genetics and phenotyping in chronic sinusitis. J Allergy Clin Immunol. 2011Oct;128(4):710-720.
72. Grigoreas C, Vourdas D, Petalas K, et al. Nasal polyps in patients with rhinitis and asthma. Allergy Asthma Proc. 2002 Jun;23(3):169-174.
73. Yılmaz İ, Türk M and Bahçecioğlu SN. Eosinophilic asthma with nasal polyposis march: Is aspirin-exacerbated respiratory disease the last station? J Allergy Clin Immunol Pract. 2017 Dec;5(6):1807-1808.
74. Rix I, Håkansson K, Larsen CG, et al. Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: a systematic review. Am J Rhinol Allergy. 2015 Jun;29(3):193-201.
75. Bousquet J, Schunemann HJ, Samolinski B, et al. Allergic Rhinitis and its Impact on

Asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol. 2012 Nov;130(5):1049-62.
76. Ragab A, Clement P and Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. Am J Rhinol. 2004 Feb;18(1):15-21.
77. Williamson P, Vaidyanathan S, Clearie K, et al. Airway dysfunction in nasal polyposis: a spectrum of asthmatic disease? Clin Exp Allergy. 2011 Oct;41(10):1379-1385.
78. Kambara R, Minami T, Akazawa H, et al. Lower Airway Inflammation in Eosinophilic Chronic Rhinosinusitis as Determined by Exhaled Nitric Oxide. Int Arch Allergy Immunol. 2017;173(4):225-232.
79. Uraguchi K, Kariya S, Makihara S, et al. Pulmonary function in patients with eosinophilic chronic rhinosinusitis. Auris Nasus Larynx. 2017 Aug 10. pii: S0385-8146(17)30373-5.
80. Bokov P, Chevalier-Bidaud B, Al Dandachi G, et al. Tracheal section is an independent predictor of asthma in patients with nasal polyposis. Respir Physiol Neurobiol. 2014 Nov 1;203:15-18.
81. Cheng YK, Tsai MH, Lin CD, et al. Oxidative stress in nonallergic nasal polyps associated with bronchial hyperresponsiveness. Allergy. 2006 Nov;61(11):1290-1298.
82. Tsicopoulos A, Shimbara A, De Nadai P, et al. Involvement of IL-9 in the bronchial phenotype of patients with nasal polyposis. J Allergy Clin Immunol. 2004 Mar;113(3):462-469.
83. Lamblin C, Bolard F, Gosset P, et al. Bronchial interleukin-5 and eotaxin expression in nasal polyposis: relationship with (a) symptomatic bronchial hyperresponsiveness. Am J Respir Crit Care Med. 2001 Apr;163(5):1226-1232.
84. Morales D, Guthrie B, Lipworth B, et al. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy. 2015 Jul;70(7):828-835.
85. Stevens WW and Schleimer RP. Aspirin-exacerbated respiratory disease as an endotype of chronic rhinosinusitis. Immunol Allergy Clin. 2016 Nov;36(4):669-680.
86. Sakalar EG, Muluk NB, Kar M, et al. Aspirin-exacerbated respiratory disease and current treatment modalities. Eur Arch Otorhinolaryngol. 2017 Mar;274(3):1291-1300.
87. Sanak M, Bochenek G, Faber J, et al. Elevated urinary leukotriene E4 excretion in asthma: a comparison of HPLC-mass spectrometry and ELISA. Allergy. 2010 May;65(5):663-664.
88. Mullol J and Picado C. Rhinosinusitis and nasal polyps in aspirin-exacerbated respiratory disease. Immunol Allergy Clin. 2013 May;33(2):163-176.
89. Stevenson DD and Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. J Allergy Clin Immunol. 2006 Oct;118(4):773-786.
90. Bavbek S, Yılmaz I, Celik G, et al. Prevalence of aspirin-exacerbated respiratory disease in patients with asthma in Turkey: a cross-sectional survey. Allergol Immunopathol (Madr). 2012 Aug;40(4):225-230.
91. Levy JM and Smith TL. Is aspirin desensitization indicated for the treatment recalcitrant chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease? Laryngoscope. 2017 Apr;127(4):776-777.
92. Levy JM, Rudmik L, Peters AT, et al. Contemporary management of chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2016 Dec;6(12):1273-1283.
93. Tajudeen BA, Schwartz JS and Bosso JV. The role of aspirin desensitization in the management of aspirin-exacerbated respiratory disease. Curr Opin Otolaryngol Head Neck Surg. 2017 Feb;25(1):30-34.
94. Jerschow E, Edin ML, Pelletier T, et al. Plasma 15-Hydroxyeicosatetraenoic Acid Predicts Treatment Outcomes in Aspirin-Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract. 2017 Aug; 5(4):998-1007. e2.
95. Laidlaw TM and Boyce JA. Aspirin-exacerbated respiratory disease—new prime suspects. N Engl J Med. 2016 Feb;374(5):484-488.
96. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol. 2015 Sep;136(3):556-568.
97. Berings M, Karaaslan C, Altunbulakli C, et al. Advances and highlights in allergen immunotherapy: On the way to sustained clinical and immunologic tolerance. J Allergy Clin Immunol. 2017 Nov;140(5):1250-1267.
98. Ehnhage A, Olsson P, Kölbeck KG, et al. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. Allergy. 2009 May;64(5):762-769.
99. Proimos E, Papadakis CE, Chimona TS, et al. The effect of functional endoscopic sinus surgery on patients with asthma and CRS with nasal polyps. Rhinology Sep. 2010(3);48:331.
100. Langdon C and Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. J Asthma Allergy. 2016 Mar;9:45-53.
101. Walgama ES and Hwang PH. Aspirin-exacerbated respiratory disease. Otolaryngol Clin North Am. 2017 Feb;50(1):83-94.
102. Wu D, Bleier BS, Li L, et al. Clinical Phenotypes of Nasal Polyps and Comorbid Asthma Based on Cluster Analysis of Disease History. J Allergy Clin Immunol Pract. 2017 Oct 31. pii: S2213-2198(17)30746-8.
103. 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 Jan;131(1):110-116. e1.
104. Bidder T, Sahota J, Rennie C, et al. Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together-a real life study. Rhinology. 2018;56(1):42-45.
105. Song WJ, Sintobin I, Sohn KH, et al. Staphylococcal enterotoxin IgE sensitization in late-onset severe eosinophilic asthma in the elderly. Clin Exp Allergy. 2016 Mar;46(3):411-421.
106. Song WJ, Chang YS, Lim MK, et al. Staphylococcal enterotoxin sensitization in a community-based population: a potential role in adult-onset asthma. Clin Exp Allergy. 2014 Apr;44(4):553-562.
107. Ilmarinen P, Tuomisto LE and Kankaanranta H. Phenotypes, risk factors, and mechanisms of adult-onset asthma. Mediators Inflamm. 2015;2015:514868.
108. Bachert C, Claeys SE, Tomassen P, et al. Rhinosinusitis and asthma: a link for asthma severity. Curr Allergy Asthma Rep. 2010 May;10(3):194-201.
109. Bachert C, Gevaert P, Van Cauwenberge P. Staphylococcus aureus enterotoxins: a key in airway disease? Allergy. 2002 Jun;57(6):480-487.
110. Bachert C, Zhang N, Krysko O, et al. Nasal polyposis and asthma: a mechanistic paradigm focusing on Staphylococcus aureus. The Nose and Sinuses in Respiratory Disorders: ERS Monograph. 2017. P. 76:122.
111. Jia G, Erickson RW, Choy DF, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol. 2012 Sep;130(3):647-654. e10.
112. Takayama G, Arima K, Kanaji T, et al. Periostin: a novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. J Allergy Clin Immunol. 2006 Jul;118(1):98-104.
113. Masuoka M, Shiraishi H, Ohta S, et al. Periostin promotes chronic allergic inflammation in response to Th2 cytokines. J Clin Invest. 2012 Jul;122(7):2590-600.
114. Scichilone N, Crimi C, Benfante A, et al. Higher serum levels of periostin and the risk of exacerbations in moderate asthmatics. Asthma Res Pract. 2016 Jan;2:1.
115. Wardzyńska A, Makowska JS, Pawełczyk M, et al. Periostin in Exhaled Breath Condensate and in Serum of Asthmatic Patients: Relationship to Upper and Lower Airway Disease. Allergy Asthma Immunol Res. 2017 Mar;9(2):126-132.
116. Nagasaki T, Matsumoto H, Kanemitsu Y, et al. Integrating longitudinal information on pulmonary function and inflammation using asthma phenotypes. J Allergy Clin Immunol. 2014 May;133(5):1474-1477. e2.
117. Asano T, Kanemitsu Y, Takemura M, et al. Serum Periostin as a Biomarker for Comorbid Chronic Rhinosinusitis in Patients with Asthma. Ann Am Thorac Soc. 2017 May;14(5):667-675.
118. Maxfield AZ, Landegger LD, Brook CD, et al. Periostin as a Biomarker for Nasal Polyps in Chronic Rhinosinusitis. Otolaryngol Head

Neck Surg. 2018 Jan;158(1):181-186.
119. Wang M, Wang X, Zhang N, et al. Association of periostin expression with eosinophilic inflammation in nasal polyps. J Allergy Clin Immunol. 2015 Dec;136(6):1700-1703. e9.
120. Miłoński J, Zielińska-Bliźniewska H, Przybyłowska K, et al. Significance of CYCLOOXYGENASE-2 (COX-2), PERIOSTIN (POSTN) and INTERLEUKIN-4 (IL-4) gene expression in the pathogenesis of chronic rhinosinusitis with nasal polyps. Eur Arch Otorhinolaryngol. 2015 Dec;272(12):3715-3720.
121. Kim M-A, Izuhara K, Ohta S, et al. Association of serum periostin with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2014 Sep;113(3):314-320.
122. Brook CD, Maxfield AZ, Stankovic K, et al. The Impact of Angiotensin-Modulating Antihypertensives on Time Interval to Revision Surgery for Nasal Polyps. Otolaryngol Head Neck Surg. 2016 Dec;155(6):1046-1052.
123. Izuhara K, Nunomura S, Nanri Y, et al. Periostin in inflammation and allergy. Cell Mol Life Sci. 2017 Dec;74(23):4293-4303.
124. Schleimer RP and Berdnikovs S. Etiology of epithelial barrier dysfunction in patients with type 2 inflammatory diseases. J Allergy Clin Immunol. 2017 Jun;139(6):1752-1761.
125. Boita M, Bucca C, Riva G, et al. Release of Type 2 Cytokines by Epithelial Cells of Nasal Polyps. J Immunol Res. 2016;2016.
126. Hammad H and Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. Immunity. 2015 Jul;43(1):29-40.
127. Pfeffer PE and Corrigan CJ. An Imbalance between Proteases and Endogenous Protease Inhibitors in Eosinophilic Airway Disease. Am J Respir Crit Care Med. 2017 Mar;195(6):707-708.
128. Gregory LG and Lloyd CM. Orchestrating house dust mite-associated allergy in the lung. Trends Immunol. 2011 Sep;32(9):402-411.
129. Stentzel S, Teufelberger A, Nordengrün M, et al. Staphylococcal serine protease–like proteins are pacemakers of allergic airway reactions to Staphylococcus aureus. J Allergy Clin Immuno. 2017 Feb;139(2):492-500.e8.
130. Teufelberger AR, Nordengrün M, Braun H, et al. The IL-33/ST2 axis is crucial in type 2 airway responses induced by the Staphylococcus aureus protease SplD. J Allergy Clin Immunol. 2018 Feb;141(2):549-559.e7.
131. Huang YJ and Boushey HA. The microbiome and asthma. Ann Am Thorac Soc. 2014 Jan;11(1):S48-S51.
132. Clark DW, Wenaas A, Luong A, et al. Staphylococcus aureus prevalence in allergic fungal rhinosinusitis vs other subsets of chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol. 2013 Feb;3(2):89-93.
133. Ou J, Wang J, Xu Y, et al. Staphylococcus aureus superantigens are associated with chronic rhinosinusitis with nasal polyps: a meta-analysis. Eur Arch Otorhinolaryngol. 2014 Oct;271(10):2729-2736.
134. Lan F, Zhang N, Gevaert E, et al. Viruses and bacteria in Th2-biased allergic airway disease. Allergy. 2016 Oct;71(10):1381-1392.
135. Wu DW, Wei Y and Bleier BS. Emerging role of Proteases in the pathogenesis of Chronic Rhinosinusitis with Nasal Polyps. Front Cell Infect Microbiol. 2017 Jan 12;7:538.
136. Pfeffer PE and Corrigan CJ. An Imbalance between Proteases and Endogenous Protease Inhibitors in Eosinophilic Airway Disease. Am J Respir Crit Care Med. 2017 Mar 15;195(6):707-708.
137. Reed CE and Kita H. The role of protease activation of inflammation in allergic respiratory diseases. J Allergy Clin Immunol. 2004 Nov;114(5):997-1008.

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