World Journal of Otorhinolaryngology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5319/wjo.v5.i2.44

World J Otorhinolaryngol 2015 May 28; 5(2): 44-52
ISSN 2218-6247 (online)

REVIEW

Relationship between chronic rhinosinusitis and lower airway diseases: An extensive review

Shin Kariya, Mitsuhiro Okano, Kazunori Nishizaki

Shin Kariya, Mitsuhiro Okano, Kazunori Nishizaki, Department of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan
Author contributions: All the authors contributed to this paper.
Supported by JSPS KAKENHI (Grants-in-Aid for Scientific Research), No. 25462642.
Conflict-of-interest: The authors have no conflict of interest to disclose.

Correspondence to: Shin Kariya, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. skariya@cc.okayama-u.ac.jp
Telephone: +81-86-2357307
Fax: +81-86-2357308
Received: October 4, 2014
Peer-review started: October 5, 2014
First decision: November 14, 2014
Revised: December 4, 2014
Accepted: March 4, 2015
Article in press: March 5, 2015
Published online: May 28, 2015

Abstract

Significant links between allergic rhinitis and asthma have been reported, and the united airway disease hypothesis is supported by numerous findings in epidemiologic, physiologic, pathologic, and immunologic studies. The impact of allergic rhinitis on asthma has been established. On the other hand, the relationship between chronic rhinosinusitis and lung diseases has been under investigation. Chronic rhinosinusitis is a common disease, and the high prevalence of chronic rhinosinusitis in some kinds of lung diseases has been reported. Recent studies suggest that the treatment of chronic rhinosinusitis has beneficial effects in the management of asthma. Here, we present an overview of the current research on the relationship between chronic rhinosinusitis and lower airway diseases including asthma, chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, primary ciliary dyskinesia, idiopathic bronchiectasis, and allergic bronchopulmonary aspergillosis.

Key words: Chronic rhinosinusitis; Sinusitis; Asthma; Chronic obstructive pulmonary disease; Cystic fibrosis; Diffuse panbronchiolitis; Primary ciliary dyskinesia; Idiopathic bronchiectasis; Allergic bronchopulmonary aspergillosis

Core tip: Chronic rhinosinusitis is a persisting inflammatory condition of the paranasal sinus. A close relationship between chronic rhinosinusitis and lower airway diseases has been suggested. The purpose of this review is to summarize recent findings on the correlation between chronic rhinosinusitis and lung diseases.

Kariya S, Okano M, Nishizaki K. Relationship between chronic rhinosinusitis and lower airway diseases: An extensive review. *World J Otorhinolaryngol* 2015; 5(2): 44-52 Available from: URL: http://www.wjgnet.com/2218-6247/full/v5/i2/44.htm DOI: http://dx.doi.org/10.5319/wjo.v5.i2.44

INTRODUCTION

Chronic rhinosinusitis is a common clinical problem, and is a complex inflammatory disease that is poorly

understood. Chronic rhinosinusitis is defined by the presence for 12 wk or longer of two or more of the following symptoms: (1) nasal blockage/obstruction/congestion; (2) nasal discharge (anterior/posterior nasal drip); (3) facial pain/pressure; and (4) reduction or loss of smell. One of these should either be nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip). The presence of endoscopic findings [(1) nasal polyps, and/or (2) mucopurulent discharge primarily from the middle meatus, and/or (3) oedema/mucosal obstruction primarily in the middle meatus] and/or mucosal changes within the ostiomeatal complex and/or sinuses revealed by computed tomography is also required[1].

According to the current consensus, chronic rhinosinusitis is subclassified into chronic rhinosinusitis without nasal polyposis (CRSsNP), chronic rhinosinusitis with nasal polyposis (CRSwNP), and allergic fungal rhinosinusitis[1-3]. Chronic rhinosinusitis has complex pathophysiological features, and the etiology of chronic rhinosinusitis is not fully understood. In immunological characteristics, CRSwNP with interleukin (IL)-5-positive cells in nasal polyps can be differentiated from CRSwNP without IL-5-positive cells by different inflammatory patterns (predominance of eosinophils *vs* neutrophils)[4].

Both pathogen exposure and host condition have significant effects on the onset of chronic rhinosinusitis. The patency of sinus ostia, normal mucociliary function, and healthy immune system are essential factors for the maintenance of normal sinus function. Mucociliary function is remarkably impaired in some diseases such as cystic fibrosis and Kartagener's syndrome (a type of primary ciliary dyskinesia). Allergic diseases and immunodeficiency may induce chronic rhinosinusitis. A close relationship between chronic rhinosinusitis and lower airway diseases has been suggested[5-9]. The purpose of this review is to summarize current understandings regarding the interaction between chronic rhinosinusitis and lower respiratory conditions. Recently, the term "rhinosinusitis" rather than "sinusitis" has been adopted because sinusitis rarely occurs in the absence of rhinitis[10,11]. In this review, rhinosinusitis and sinusitis are used synonymously.

ASTHMA

The relationship between allergic rhinitis and asthma is now established, and numerous clinical, epidemiological, and biological studies recommend integrated management[12,13]. In the past few decades, the association between chronic rhinosinusitis and asthma has come to be recognized. The presence of rhinosinusitis is associated with more severe asthmatic symptoms in patients with asthma[14]. In epidemiological and radiographic studies, 40% to 90% of asthmatic patients presented abnormal findings on CT scans of their sinuses[15-18].

Several explanations for the association of chronic rhinosinusitis and asthma including the naso-bronchial reflex, pharyngo-bronchial reflex, postnasal drainage of inflammatory mediators from the upper to lower airway, inhalation of dry, cold air and environmental pollutants, and the "shared pathogenesis" of chronic rhinosinusitis and asthma are proposed. The naso-bronchial reflex is mediated by afferent pathways involving the trigeminal nerve and efferent fibers causing bronchoconstriction by means of the vagus nerve. The irritant in the nasal cavity has led to efferent bronchoconstriction[16]. However, the exact mechanisms linking chronic rhinosinusitis and asthma are under debate[19,20].

Severe mucosal inflammation with immune dysregulation is a common feature of chronic rhinosinusitis and asthma[21]. The immunological findings including IL-17, IL-18, IL-25, IL-33, toll-like receptors (TLRs), and thymic stromal lymphopoietin (TSLP) are similar in chronic rhinosinusitis and asthma[22-24]. Transforming growth factor (TGF)-β1 is a major participant in the airway remodeling of asthma, and is also known to play an important role in the tissue remodeling processes and enhanced epithelial immunoreactivity involved in chronic rhinosinusitis[25]. Because the enhanced TGF-β signaling in CRSsNP and reduced TGF-β signaling in CRSwNP is compatible with the remodeling patterns observed in the disease subgroups, TGF-β is characterized as a key switch between CRSsNP and CRSwNP[4]. More than 80% of nasal polyps in Caucasians express IL-5 protein, and more than 50% are eosinophilic, whereas in the Chinese group that was studied, less than 20% express IL-5 protein and less than 10% are eosinophilic[26]. The prevalence of allergic rhinitis, a typical immunoglobulin E (IgE)-mediated type Ⅰ allergic disease, has been increasing in African continent[27,28]. Allergic rhinitis is significantly more common among asthmatic subjects (76%) than among nonasthmatic subjects (48%) in urban Ghana[29]. The role of IL-5 and eosinophils in chronic rhinosinusitisin in African subjects has not been reported to date, however allergy is the commonest etiological factors for chronic rhinosinusitisin in Nigeria[30]. Although regional differences have been reported, IL-5, a strong secretagogue for human eosinophils, and IgE, specifically IgE against staphylococcal enterotoxins, are identified as indicators of asthma comorbidity in a group of patients with CRSwNP[31].

Blood and sputum eosinophil levels in patients with asthma are directly correlated with sinus mucosal thickening as assessed by computed tomography (CT) scanning[32]. The link between chronic rhinosinusitis and asthma is not only of academic interest, but also an important factor in diagnostic and therapeutic strategy. Asthma phenotypes are very heterogeneous, and inflammation can be predominantly eosinophilic or neutrophilic[33]. Increasing evidence suggests that patients with chronic rhinosinusitis should be evaluated for possible concomitant asthma, and that patients with asthma should always be evaluated for possible nasal and paranasal disease. Both medical and surgical treatments of chronic rhinosinusitis benefit concomitant asthma[34-37]. Although an opposite opinion

has been held[38], functional endoscopic sinus surgery is suggested for asthmatic patients including children in whom appropriate medical therapy has failed to resolve sinus disease[39-41].

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic respiratory diseases. Smoking is the primary risk factor for COPD. The coexistence of upper airway diseases with COPD is not well documented, and only a few authors have studied the role of chronic rhinosinusitis in COPD. Although the available data are limited, a certain relationship between sinonasal disorders and COPD has been suggested[42]. In epidemiological studies, patients with an established diagnosis of COPD have a significantly higher incidence of rhinosinusitis as compared with age-matched control subjects (12.4% *vs* 2.5%; OR = 6.08; 95%CI: 2.87-12.89)[43]. Another recent study supports these findings[44]. The potential hypotheses for interaction between the upper and lower airways in COPD patients are (1) loss of nasal conditioning function; (2) direct passage of inflammatory mediators and/or microorganisms between upper and lower respiratory tracts; (3) nasobronchial neuronal reflexes; (4) stimulation at one point of the respiratory mucosal surface resulting in a pan-airway inflammatory response; and (5) inflammation caused by smoking[42,45].

Numerous cytokines, chemokines, and other inflammatory factors including TGF-β, tumor necrosis factor-alpha (TNF-α), interferon gamma (IFN-γ), IL-1β, IL-6, IL-8, IL-18, chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-X-C motif) ligand 9 (CXCL9), CXCL10, and CXCL11 are involved in COPD[46]. A physiological study using spirometry and acoustic rhinometry showed a significant relationship between nasal patency and pulmonary airflow obstruction in COPD[47]. In immunological studies, COPD has been associated with an increased level of IL-8, a potent neutrophil chemoattractant, in nasal secretion, and patients with COPD have higher nasal concentrations of eotaxin, granulocyte-colony stimulating factor (G-CSF), and IFN-γ than controls[48,49].

Cigarette smoking is the main cause of COPD, and it also induces sinonasal inflammation[50-53]. Smoking is associated with inflammation throughout the airway. The evidence from previous studies provides conflicting data on the relationship between rhinosinusitis and COPD severity. A recent study showed that clinical symptoms, endoscopic score, saccharine test results, cellular profile of nasal lavage, and levels of eicosanoids in nasal lavage in chronic rhinosinusitis patients are not different between COPD stages, and concluded that sinonasal inflammation is not strictly related to COPD severity[54]. Although the coexistence of COPD and chronic rhinosinusitis is frequently observed, further studies are needed to explain the causative role of chronic rhinosinusitis in COPD.

CYSTIC FIBROSIS

Cystic fibrosis is an inherited disease caused by genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes for an ATP-regulated ion-channel, which is expressed in many tissues. Although several therapeutic agents have been developed in recent years, no curative therapy exists for cystic fibrosis[55]. Gene therapy is an attractive approach, however the difficulty of gene therapy is reflected by the variable results of the 25 gene therapy trials for cystic fibrosis[55]. Gene therapy using non-viral vectors or viral vectors is actively investigated, however no current gene therapy trial is actively enrolling patients. Because the surface fluid in cystic fibrosis patients has a high NaCl concentration due to dysfunction of the CFTR Cl^- channel, cystic fibrosis airway epithelia fail to kill pathogens[56]. Chronic rhinosinusitis with or without nasal polyposis is common in patients with cystic fibrosis[57,58]. Nasal polyps are present in approximately 40% of chronic rhinosinusitis patients with cystic fibrosis, and the polyps exhibit predominantly neutrophilic, rather than eosinophilic, inflammation[59].

Numerous bacteria are frequently isolated from sinus cultures of chronic rhinosinusitis patients with cystic fibrosis; *Pseudomonas aeruginosa* as well as *Staphylococcus aureus* are the most common bacterial species[60]. The same pathogen is commonly found in both the upper and lower respiratory tracts in chronic rhinosinusitis patients with cystic fibrosis, and genotypes of sinus bacteria are shown to be consistent with those in the lower airway, indicating that the nasal cavity and paranasal sinuses may serve as bacterial reservoirs for recurrent lung infection[61].

The management of chronic rhinosinusitis in patients with cystic fibrosis is difficult. Medical management usually consists of daily nasal care, nasal saline irrigations, surfactant lavage, and medications. Oral or intravenous antibiotics, decongestants, antihistamines, topical and/or systemic steroids, dornase alfa, ibuprofen, and N-acetyl cysteine are used as therapeutic agents[62]. Surgical management is indicated for patients who fail medical management. Surgical management of the sinuses in cystic fibrosis patients may improve lower airway outcomes. However, no definitive effect of endoscopic sinus surgery on lung infection has been established[63]. Multiple studies have shown the safety and effectiveness of endoscopic sinus surgery for chronic rhinosinusitis in cystic fibrosis patients. However, overall failure rates requiring revision surgery are high (13% to 89%)[64-70].

Sinus diseases should be routinely evaluated by diagnostic testing (*i.e.*, CT scan) in patients with cystic fibrosis because chronic rhinosinusitis could be a source for lower airway infection[71,72].

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis (DPB) is characterized by chronic sinobronchial inflammation, and is a treatable neutrophil-related pulmonary disease. DPB was originally found in Asian populations, and has recently been encountered in Western countries, both clinically and pathologically[73-78]. In DPB, no association with smoking or exposure to fumes or toxic agents has been proven. Human leukocyte antigen (HLA) alleles (HLA-B54 and HLA-A11) are thought to be causal factors for a genetic predisposition to DPB, and these findings suggest a major HLA susceptibility gene for DPB. Untreated DPB generally progresses to bronchiectasis, with resultant respiratory failure and death[79].

Patients with DPB have a history of chronic rhinosinusitis or still have the disease[75,80]. Significant improvement of DPB and concomitant chronic rhinosinusitis has been reported after the use of long-term therapy with macrolide antibiotics[81,82]. Before the 1970s, the prognosis of patients with DPB was poor, with 10-year survival rates of under 40%. However, after the 1980s, long-term erythromycin treatment has increased the 10-year survival rate to over 90%[83].

The mechanisms of the anti-inflammatory properties of macrolides are still being investigated. Macrolides inhibit the production of many proinflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF-β, by suppressing transcription factors including nuclear factor-kappa B and/or activator protein-1[84,85]. It is highly recommended that chronic rhinosinusitis in patients with DPB be treated with 14- and 15-membered macrolides.

PRIMARY CILIARY DYSKINESIA

Primary ciliary dyskinesia is a rare, genetically heterogeneous autosomal recessive disorder characterized by ciliary dysfunction and impaired mucociliary clearance[86]. The clinical effects of primary ciliary dyskinesia include recurrent lower airway infection, bronchiectasis, male infertility, otitis media with effusion, rhinitis, and rhinosinusitis[87-89]. Otitis media with effusion is considered the most common otolaryngologic manifestation of primary ciliary dyskinesia, affecting up to 85% of children with primary ciliary dyskinesia. Chronic rhinitis and chronic rhinosinusitis are found in almost all primary ciliary dyskinesia patients[90,91].

Sinonasal disease in primary ciliary dyskinesia is poorly understood[92]. The prevalence of nasal polyps in chronic rhinosinusitis patients with primary ciliary dyskinesia is low (15% to 30%), and nasal polyps are rarely observed in pediatric patients[93-96]. In the management of the lower airway tract, macrolide therapy has no effect in primary ciliary dyskinesia[81]. Saline nasal irrigation, longterm macrolide therapy, and endoscopic sinus surgery may be beneficial for primary ciliary dyskinesia patients with intractable chronic rhinosinusitis[96-98]. Nasal symptoms usually consist of persistent nasal discharge and blockage; sinus surgery may not be effective in reducing nasal discharge[99]. Because of the lack of evidence in the literature, any surgical intervention should be followed by noninvasive management of chronic rhinosinusitis[90].

IDIOPATHIC BRONCHIECTASIS

Bronchiectasis is defined as abnormal and irreversibly dilated bronchi caused by the loss of the elastic and muscular components of the bronchial and peribronchial tree following recurrent lower airway infection. Bronchiectasis is the result of several different etiologies including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency, tuberculosis, graft-*vs*-host disease, and inflammatory bowel diseases. The most common causes of bronchiectasis are idiopathic and post-infective damage[87,100]. Regardless of the underlying cause, inflammation in bronchiectasis is predominantly neutrophil driven[101].

Chronic rhinosinusitis was found in 45% to 84% of the cases of patients with idiopathic bronchiectasis[102,103]. A recent study reported a possible association between bronchiectasis and chronic rhinosinusitis[104]. Because the available data is limited, the clinical, histopathological, and immunological characteristics of chronic rhinosinusitis in patients with idiopathic bronchiectasis are largely unknown.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a Th2 hypersensitivity lung disease, and is one of the frequent forms of allergic bronchopulmonary mycosis. ABPA is commonly caused by bronchial colonization with *Aspergillus fumigatus*[105]. *A. fumigatus* affects approximately 0.7% to 3.5% of asthmatic patients and 7% to 9% of patients with cystic fibrosis[106-108]. Up to 50% of patients with acute severe asthma has *A. fumigatus* hypersensitivity, and 7% to 15% of cystic fibrosis patients have ABPA[108-111]. Patients with *A. fumigatus*-mediated chronic asthma or ABPA in cystic fibrosis showed significantly decreased pulmonary function leading to poorer outcomes[112-115]. In addition, antifungal therapy leads to better lung function in *A. fumigatus*-sensitized cystic fibrosis patients[116].

Allergic fungal rhinosinusitis (AFRS) is a noninvasive form of fungal chronic rhinosinusitis, and has IgE-mediated type I hypersensitivity to fungal proteins[117]. Dematiaceous fungi (such as *Bipolaris spicifera* or *Curvularia lunata*) or Aspergillus species (such as *A. fumigatus*, *A. niger*, or *A. flavus*) are commonly detected in allergic mucin, which is the characteristic extramucosal "peanut buttery" viscoelastic, eosinophil-rich material in AFRS[118]. The serological findings of Bipolaris spicifera in AFRS are analogous to those seen with *A. fumigatus* in ABPA[119]. AFRS has similar

clinicopathological features to those in ABPA. However, immunological hypersensitivity is less intense in AFRS compared to that in ABPA[120].

Conflicting opinions have been reported in the incidence of the coexistence of allergic bronchopulmonary fungal disease and AFRS[121,122]. There is a lack of data on the causative and pathophysiologic relationship between ABPA and AFRS, and it has not been proven whether the postnasal drainage of Aspergillus-containing mucus into the lower airways influences the development or severity of ABPA[123]. Postoperative systemic and/or standard topical nasal steroids are recommended in the medical management of AFRS[124]. Further studies are needed to assess relationships in the etiology and management strategy of ABPA and AFRS.

CONCLUSION

To date, numerous studies have been reported about the relationship between upper and lower airway diseases[125]. Chronic rhinosinusitis is frequently coexistent with lung diseases, and has a causative role in the onset and development of chronic lower respiratory diseases. Appropriate assessment and treatment in the upper respiratory tract are necessary to manage united airway diseases.

REFERENCES

1 **Fokkens WJ**, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang de Y, Wormald PJ. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012; **50**: 1-12 [PMID: 22469599 DOI: 10.4193/Rhino50E2]

2 **Hamilos DL**. Chronic rhinosinusitis: epidemiology and medical management. *J Allergy Clin Immunol* 2011; **128**: 693-707; quiz 708-709 [PMID: 21890184 DOI: 10.1016/j.jaci.2011.08.004]

3 **Dykewicz MS**, Hamilos DL. Rhinitis and sinusitis. *J Allergy Clin Immunol* 2010; **125**: S103-S115 [PMID: 20176255 DOI: 10.1016/j.jaci.2009.12.989]

4 **Bachert C**, Claeys SE, Tomassen P, van Zele T, Zhang N. Rhinosinusitis and asthma: a link for asthma severity. *Curr Allergy Asthma Rep* 2010; **10**: 194-201 [PMID: 20424997 DOI: 10.1007/s11882-010-0096-0]

5 **Feng CH**, Miller MD, Simon RA. The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis. *Am J Rhinol Allergy* 2012; **26**: 187-190 [PMID: 22643942 DOI: 10.2500/ajra.2012.26.3762]

6 **Hellings PW**, Hens G. Rhinosinusitis and the lower airways. *Immunol Allergy Clin North Am* 2009; **29**: 733-740 [PMID: 19879447 DOI: 10.1016/j.iac.2009.08.001]

7 **Hens G**, Hellings PW. The nose: gatekeeper and trigger of bronchial disease. *Rhinology* 2006; **44**: 179-187 [PMID: 17020064]

8 **Kariya S**, Okano M, Oto T, Higaki T, Makihara S, Haruna T, Nishizaki K. Pulmonary function in patients with chronic rhinosinusitis and allergic rhinitis. *J Laryngol Otol* 2014; **128**: 255-262 [PMID: 24621450 DOI: 10.1017/S0022215114000450]

9 **Kariya S**, Okano M, Higaki T, Noyama Y, Haruna T, Ishihara H, Makino T, Onoda T, Nishizaki K. Chronic rhinosinusitis patients have decreased lung function. *Int Forum Allergy Rhinol* 2014; **4**: 828-833 [PMID: 25132678 DOI: 10.1002/alr.21370]

10 **Meltzer EO**, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, Bachert C, Baraniuk J, Baroody FM, Benninger MS, Brook I, Chowdhury BA, Druce HM, Durham S, Ferguson B, Gwaltney JM, Kaliner M, Kennedy DW, Lund V, Naclerio R, Pawankar R, Piccirillo JF, Rohane P, Simon R, Slavin RG, Togias A, Wald ER, Zinreich SJ. Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol* 2004; **114**: 155-212 [PMID: 15577865 DOI: 10.1016/j.jaci.2004.09.029]

11 **Lanza DC**, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997; **117**: S1-S7 [PMID: 9334782 DOI: 10.1016/S0194-5998(97)70001-9]

12 **Bourdin A**, Gras D, Vachier I, Chanez P. Upper airway x 1: allergic rhinitis and asthma: united disease through epithelial cells. *Thorax* 2009; **64**: 999-1004 [PMID: 19864543 DOI: 10.1136/thx.2008.112862]

13 **Bousquet J**, Schünemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, Bonini S, Boulet LP, Bousquet PJ, Brozek JL, Canonica GW, Casale TB, Cruz AA, Fokkens WJ, Fonseca JA, van Wijk RG, Grouse L, Haahtela T, Khaltaev N, Kuna P, Lockey RF, Lodrup Carlsen KC, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Palkonen S, Papadopoulos NG, Passalacqua G, Pawankar R, Price D, Ryan D, Simons FE, Togias A, Williams D, Yorgancioglu A, Yusuf OM, Aberer W, Adachi M, Agache I, Aït-Khaled N, Akdis CA, Andrianarisoa A, Annesi-Maesano I, Ansotegui IJ, Baiardini I, Bateman ED, Bedbrook A, Beghé B, Beji M, Bel EH, Ben Kheder A, Bennoor KS, Bergmann KC, Berrissoul F, Bieber T, Bindslev Jensen C, Blaiss MS, Boner AL, Bouchard J, Braido F, Brightling CE, Bush A, Caballero F, Calderon MA, Calvo MA, Camargos PA, Caraballo LR, Carlsen KH, Carr W, Cepeda AM, Cesario A, Chavannes NH, Chen YZ, Chiriac AM, Chivato Pérez T, Chkhartishvili E, Ciprandi G, Costa DJ, Cox L, Custovic A, Dahl R, Darsow U, De Blay F, Deleanu D, Denburg JA, Devillier P, Didi T, Dokic D, Dolen WK, Douagui H, Dubakiene R, Durham SR, Dykewicz MS, El-Gamal Y, El-Meziane A, Emuzyte R, Fiocchi A, Fletcher M, Fukuda T, Gamkrelidze A, Gereda JE, González Diaz S, Gotua M, Guzmán MA, Hellings PW, Hellquist-Dahl B, Horak F, Hourihane JO, Howarth P, Humbert M, Ivancevich JC, Jackson C, Just J, Kalayci O, Kaliner MA, Kalyoncu AF, Keil T, Keith PK, Khayat G, Kim YY, Koffi N'goran B, Koppelman GH, Kowalski ML, Kull I, Kvedariene V, Larenas-Linnemann D, Le LT, Lemière C, Li J, Lieberman P, Lipworth B, Mahboub B, Makela MJ, Martin F, Marshall GD, Martinez FD, Masjedi MR, Maurer M, Mavale-Manuel S, Mazon A, Melen E, Meltzer EO, Mendez NH, Merk H, Mihaltan F, Mohammad Y, Morais-Almeida M, Muraro A, Nafti S, Namazova-Baranova L, Nekam K, Neou A, Niggemann B, Nizankowska-Mogilnicka E, Nyembue TD, Okamoto Y, Okubo K, Orru MP, Ouedraogo S, Ozdemir C, Panzner P, Pali-Schöll I, Park HS, Pigearias B, Pohl W, Popov TA, Postma DS, Potter P, Rabe KF, Ratomaharo J, Reitamo S, Ring J, Roberts R, Rogala B, Romano A, Roman Rodriguez M, Rosado-Pinto J, Rosenwasser L, Rottem M, Sanchez-Borges M, Scadding GK, Schmid-Grendelmeier P, Sheikh A, Sisul JC, Solé D, Sooronbaev T, Spicak V, Spranger O, Stein RT, Stoloff SW, Sunyer J, Szczeklik A, Todo-Bom A, Toskala E, Tremblay Y, Valenta R, Valero AL, Valeyre D, Valiulis A, Valovirta E, Van Cauwenberge P, Vandenplas O, van Weel C, Vichyanond P, Viegi G, Wang DY, Wickman M, Wöhrl S, Wright J, Yawn BP, Yiallouros PK, Zar HJ, Zernotti ME, Zhong N, Zidarn M, Zuberbier T, Burney PG, Johnston SL, Warner JO; World Health Organization Collaborating Center for Asthma and Rhinitis. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* 2012; **130**: 1049-1062 [PMID: 23040884 DOI: 10.1016/j.jaci.2012.07.053]

14 **Dixon AE**, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. *Chest* 2006; **130**: 429-435 [PMID: 16899841 DOI: 10.1378/chest.130.2.429]

15 **Meltzer EO**, Szwarcberg J, Pill MW. Allergic rhinitis, asthma, and rhinosinusitis: diseases of the integrated airway. *J Manag Care Pharm* 2004; **10**: 310-317 [PMID: 15298529]

16 **Joe SA**, Thakkar K. Chronic rhinosinusitis and asthma. *Otolaryngol*

Clin North Am 2008; **41**: 297-309, vi [PMID: 18328369 DOI: 10.1016/j.otc.2007.11.001]
17 **Bresciani M**, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, Bousquet J, Chanez P. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001; **107**: 73-80 [PMID: 11149994 DOI: 10.1067/mai.2001.111593]
18 **ten Brinke A**, Grootendorst DC, Schmidt JT, De Bruïne FT, van Buchem MA, Sterk PJ, Rabe KF, Bel EH. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002; **109**: 621-626 [PMID: 11941310 DOI: 10.1067/mai.2002.122458]
19 **Ciprandi G**, Caimmi D, Miraglia Del Giudice M, La Rosa M, Salpietro C, Marseglia GL. Recent developments in United airways disease. *Allergy Asthma Immunol Res* 2012; **4**: 171-177 [PMID: 22754709 DOI: 10.4168/aair.2012.4.4.171]
20 **Slavin RG**. The upper and lower airways: the epidemiological and pathophysiological connection. *Allergy Asthma Proc* 2008; **29**: 553-556 [PMID: 19173781 DOI: 10.2500/aap.2008.29.3169]
21 **Suzaki H**, Watanabe S, Pawankar R. Rhinosinusitis and asthma-microbiome and new perspectives. *Curr Opin Allergy Clin Immunol* 2013; **13**: 45-49 [PMID: 23128418 DOI: 10.1097/ACI.0b013e32835b34f6]
22 **Kariyawasam HH**, Rotiroti G. Allergic rhinitis, chronic rhinosinusitis and asthma: unravelling a complex relationship. *Curr Opin Otolaryngol Head Neck Surg* 2013; **21**: 79-86 [PMID: 23241653 DOI: 10.1097/MOO.0b013e32835ac640]
23 **Oda H**, Kawayama T, Imaoka H, Sakazaki Y, Kaku Y, Okamoto M, Kitasato Y, Edakuni N, Takenaka S, Yoshida M, Iwanaga T, Kato S, O'Byrne PM, Hoshino T. Interleukin-18 expression, CD8(+) T cells, and eosinophils in lungs of nonsmokers with fatal asthma. *Ann Allergy Asthma Immunol* 2014; **112**: 23-28.e1 [PMID: 24331389 DOI: 10.1016/j.anai.2013.09.004]
24 **Okano M**, Fujiwara T, Makihara S, Fujiwara R, Higaki T, Kariya S, Noda Y, Haruna T, Nishizaki K. Characterization of IL-18 expression and release in the pathogenesis of chronic rhinosinusitis. *Int Arch Allergy Immunol* 2013; **160**: 275-286 [PMID: 23075512 DOI: 10.1159/000341668]
25 **Frieri M**. Asthma linked with rhinosinusitis: An extensive review. *Allergy Rhinol* (Providence) 2014; **5**: 41-49 [PMID: 24684837 DOI: 10.2500/ar.2014.5.0083]
26 **Bachert C**, Zhang N, Holtappels G, De Lobel L, van Cauwenberge P, Liu S, Lin P, Bousquet J, Van Steen K. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. *J Allergy Clin Immunol* 2010; **126**: 962-968, 962-968 [PMID: 20810157 DOI: 10.1016/j.jaci.2010.07.007]
27 **Zar HJ**, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol* 2007; **18**: 560-565 [PMID: 18001427 DOI: 10.1111/j.1399-3038.2007.00554.x]
28 **Nyembue TD**, Ntumba W, Omadjela LA, Muyunga C, Hellings PW, Jorissen M. Sensitization rate and clinical profile of Congolese patients with rhinitis. *Allergy Rhinol* (Providence) 2012; **3**: e16-e24 [PMID: 22852125 DOI: 10.2500/ar.2012.3.0023]
29 **Addo-Yobo EO**, Custovic A, Taggart SC, Craven M, Bonnie B, Woodcock A. Risk factors for asthma in urban Ghana. *J Allergy Clin Immunol* 2001; **108**: 363-368 [PMID: 11544454 DOI: 10.1067/mai.2001.117464]
30 **Iseh KR**, Makusidi M. Rhinosinusitis: a retrospective analysis of clinical pattern and outcome in north western Nigeria. *Ann Afr Med* 2010; **9**: 20-26 [PMID: 20418645 DOI: 10.4103/1596-3519.62620]
31 **Bachert C**, Zhang N. Chronic rhinosinusitis and asthma: novel understanding of the role of IgE 'above atopy'. *J Intern Med* 2012; **272**: 133-143 [PMID: 22640264 DOI: 10.1111/j.1365-2796.2012.02559.x]
32 **Mehta V**, Campeau NG, Kita H, Hagan JB. Blood and sputum eosinophil levels in asthma and their relationship to sinus computed tomographic findings. *Mayo Clin Proc* 2008; **83**: 671-678 [PMID: 18533084 DOI: 10.4065/83.6.671]
33 **Frey U**, Suki B. Complexity of chronic asthma and chronic obstructive pulmonary disease: implications for risk assessment, and disease progression and control. *Lancet* 2008; **372**: 1088-1099 [PMID: 18805337 DOI: 10.1016/S0140-6736(08)61450-6]
34 **Ragab S**, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J* 2006; **28**: 68-74 [PMID: 16510462 DOI: 10.1183/09031936.06.00043305]
35 **Ikeda K**, Tanno N, Tamura G, Suzuki H, Oshima T, Shimomura A, Nakabayashi S, Takasaka T. Endoscopic sinus surgery improves pulmonary function in patients with asthma associated with chronic sinusitis. *Ann Otol Rhinol Laryngol* 1999; **108**: 355-359 [PMID: 10214782 DOI: 10.1177/000348949910800407]
36 **Batra PS**, Kern RC, Tripathi A, Conley DB, Ditto AM, Haines GK, Yarnold PR, Grammar L. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. *Laryngoscope* 2003; **113**: 1703-1706 [PMID: 14520093 DOI: 10.1097/00005537-200310000-00008]
37 **Manning SC**, Wasserman RL, Silver R, Phillips DL. Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma. *Arch Otolaryngol Head Neck Surg* 1994; **120**: 1142-1145 [PMID: 7917197 DOI: 10.1001/archotol.1994.01880340082014]
38 **Goldstein MF**, Grundfast SK, Dunsky EH, Dvorin DJ, Lesser R. Effect of functional endoscopic sinus surgery on bronchial asthma outcomes. *Arch Otolaryngol Head Neck Surg* 1999; **125**: 314-319 [PMID: 10190804 DOI: 10.1001/archotol.125.3.314]
39 **de Benedictis FM**, Bush A. Rhinosinusitis and asthma: epiphenomenon or causal association? *Chest* 1999; **115**: 550-556 [PMID: 10027458 DOI: 10.1378/chest.115.2.550]
40 **Senior BA**, Kennedy DW. Management of sinusitis in the asthmatic patient. *Ann Allergy Asthma Immunol* 1996; **77**: 6-15; quiz 15-19 [PMID: 8705638 DOI: 10.1016/S1081-1206(10)63473-4]
41 **Lai L**, Hopp RJ, Lusk RP. Pediatric chronic sinusitis and asthma: a review. *J Asthma* 2006; **43**: 719-725 [PMID: 17169821 DOI: 10.1080/02770900600620269]
42 **Hurst JR**. Upper airway. 3: Sinonasal involvement in chronic obstructive pulmonary disease. *Thorax* 2010; **65**: 85-90 [PMID: 20029042 DOI: 10.1136/thx.2008.112888]
43 **van Manen JG**, Bindels PJ, IJzermans CJ, van der Zee JS, Bottema BJ, Schadé E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol* 2001; **54**: 287-293 [PMID: 11223326 DOI: 10.1016/S0895-4356(01)00346-8]
44 **Kelemence A**, Abadoglu O, Gumus C, Berk S, Epozturk K, Akkurt I. The frequency of chronic rhinosinusitis/nasal polyp in COPD and its effect on the severity of COPD. *COPD* 2011; **8**: 8-12 [PMID: 21299473 DOI: 10.3109/15412555.2010.540272]
45 **Kim JS**, Rubin BK. Nasal and sinus inflammation in chronic obstructive pulmonary disease. *COPD* 2007; **4**: 163-166 [PMID: 17530509 DOI: 10.1080/15412550701341228]
46 **Barnes PJ**. The cytokine network in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 2008; **118**: 3546-3556 [PMID: 18982161 DOI: 10.1172/JCI36130]
47 **Hurst JR**, Kuchai R, Michael P, Perera WR, Wilkinson TM, Wedzicha JA. Nasal symptoms, airway obstruction and disease severity in chronic obstructive pulmonary disease. *Clin Physiol Funct Imaging* 2006; **26**: 251-256 [PMID: 16836700 DOI: 10.1111/j.1475-097X.2006.00683.x]
48 **Hurst JR**, Wilkinson TM, Perera WR, Donaldson GC, Wedzicha JA. Relationships among bacteria, upper airway, lower airway, and systemic inflammation in COPD. *Chest* 2005; **127**: 1219-1226 [PMID: 15821198 DOI: 10.1378/chest.127.4.1219]
49 **Hens G**, Vanaudenaerde BM, Bullens DM, Piessens M, Decramer M, Dupont LJ, Ceuppens JL, Hellings PW. Sinonasal pathology in nonallergic asthma and COPD: 'united airway disease' beyond the scope of allergy. *Allergy* 2008; **63**: 261-267 [PMID: 18053011 DOI: 10.1111/j.1398-9995.2007.01545.x]
50 **Reh DD**, Higgins TS, Smith TL. Impact of tobacco smoke on chronic rhinosinusitis: a review of the literature. *Int Forum Allergy Rhinol* 2012; **2**: 362-369 [PMID: 22696460 DOI: 10.1002/alr.21054]
51 **Berania I**, Endam LM, Filali-Mouhim A, Boisvert P, Boulet

LP, Bossé Y, Desrosiers M. Active smoking status in chronic rhinosinusitis is associated with higher serum markers of inflammation and lower serum eosinophilia. *Int Forum Allergy Rhinol* 2014; **4**: 347-352 [PMID: 24431239 DOI: 10.1002/alr.21289]

52 **Hur K**, Liang J, Lin SY. The role of secondhand smoke in sinusitis: a systematic review. *Int Forum Allergy Rhinol* 2014; **4**: 22-28 [PMID: 24574074 DOI: 10.1002/alr.21232]

53 **Lee KI**, Kim DW, Kim EH, Kim JH, Samivel R, Kwon JE, Ahn JC, Chung YJ, Mo JH. Cigarette smoke promotes eosinophilic inflammation, airway remodeling, and nasal polyps in a murine polyp model. *Am J Rhinol Allergy* 2014; **28**: 208-214 [PMID: 24980232 DOI: 10.2500/ajra.2014.28.4055]

54 **Piotrowska VM**, Piotrowski WJ, Kurmanowska Z, Marczak J, Górski P, Antczak A. Rhinosinusitis in COPD: symptoms, mucosal changes, nasal lavage cells and eicosanoids. *Int J Chron Obstruct Pulmon Dis* 2010; **5**: 107-117 [PMID: 20631813 DOI: 10.2147/COPD.S8862]

55 **Hoffman LR**, Ramsey BW. Cystic fibrosis therapeutics: the road ahead. *Chest* 2013; **143**: 207-213 [PMID: 23276843 DOI: 10.1378/chest.12-1639]

56 **Smith JJ**, Travis SM, Greenberg EP, Welsh MJ. Cystic fibrosis airway epithelia fail to kill bacteria because of abnormal airway surface fluid. *Cell* 1996; **85**: 229-236 [PMID: 8612275 DOI: 10.1016/S0092-8674(00)81099-5]

57 **Smyth AR**, Bell SC, Bojcin S, Bryon M, Duff A, Flume P, Kashirskaya N, Munck A, Ratjen F, Schwarzenberg SJ, Sermet-Gaudelus I, Southern KW, Taccetti G, Ullrich G, Wolfe S. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *J Cyst Fibros* 2014; **13** Suppl 1: S23-S42 [PMID: 24856775 DOI: 10.1016/j.jcf.2014.03.010]

58 **Farrell PM**, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, Durie PR, Legrys VA, Massie J, Parad RB, Rock MJ, Campbell PW 3rd; Cystic Fibrosis Foundation. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 2008; **153**: S4-S14 [PMID: 18639722 DOI: 10.1016/j.jpeds.2008.05.005]

59 **Ooi EH**, Psaltis AJ, Witterick IJ, Wormald PJ. Innate immunity. *Otolaryngol Clin North Am* 2010; **43**: 473-487, vii [PMID: 20525504 DOI: 10.1016/j.otc.2010.02.020]

60 **Muhlebach MS**, Miller MB, Moore C, Wedd JP, Drake AF, Leigh MW. Are lower airway or throat cultures predictive of sinus bacteriology in cystic fibrosis? *Pediatr Pulmonol* 2006; **41**: 445-451 [PMID: 16547960 DOI: 10.1002/ppul.20396]

61 **Mainz JG**, Koitschev A. Management of chronic rhinosinusitis in CF. *J Cyst Fibros* 2009; **8** Suppl 1: S10-S14 [PMID: 19460681 DOI: 10.1016/S1569-1993(09)60005-9]

62 **Chaaban MR**, Kejner A, Rowe SM, Woodworth BA. Cystic fibrosis chronic rhinosinusitis: a comprehensive review. *Am J Rhinol Allergy* 2013; **27**: 387-395 [PMID: 24119602 DOI: 10.2500/ajra.2013.27.3919]

63 **Liang J**, Higgins TS, Ishman SL, Boss EF, Benke JR, Lin SY. Surgical management of chronic rhinosinusitis in cystic fibrosis: a systematic review. *Int Forum Allergy Rhinol* 2013; **3**: 814-822 [PMID: 23839953 DOI: 10.1002/alr.21190]

64 **Schulte DL**, Kasperbauer JL. Safety of paranasal sinus surgery in patients with cystic fibrosis. *Laryngoscope* 1998; **108**: 1813-1815 [PMID: 9851496 DOI: 10.1097/00005537-199812000-00009]

65 **Cuyler JP**. Follow-up of endoscopic sinus surgery on children with cystic fibrosis. *Arch Otolaryngol Head Neck Surg* 1992; **118**: 505-506 [PMID: 1571123 DOI: 10.1001/archotol.1992.01880050057013]

66 **Albritton FD**, Kingdom TT. Endoscopic sinus surgery in patients with cystic fibrosis: an analysis of complications. *Am J Rhinol* 2000; **14**: 379-385 [PMID: 11197114 DOI: 10.2500/105065800779954338]

67 **Rowe-Jones JM**, Mackay IS. Endoscopic sinus surgery in the treatment of cystic fibrosis with nasal polyposis. *Laryngoscope* 1996; **106**: 1540-1544 [PMID: 8948619 DOI: 10.1097/00005537-199612000-00019]

68 **Van Peteghem A**, Clement PA. Influence of extensive functional endoscopic sinus surgery (FESS) on facial growth in children with cystic fibrosis. Comparison of 10 cephalometric parameters of the midface for three study groups. *Int J Pediatr Otorhinolaryngol* 2006; **70**: 1407-1413 [PMID: 16621034 DOI: 10.1016/j.ijporl.2006.02.009]

69 **Jaffe BF**, Strome M, Khaw KT, Shwachman H. Nasal polypectomy and sinus surgery for cystic fibrosis--a 10 year review. *Otolaryngol Clin North Am* 1977; **10**: 81-90 [PMID: 854356]

70 **Yung MW**, Gould J, Upton GJ. Nasal polyposis in children with cystic fibrosis: a long-term follow-up study. *Ann Otol Rhinol Laryngol* 2002; **111**: 1081-1086 [PMID: 12498368 DOI: 10.1177/000348940211101204]

71 **Chang EH**. New insights into the pathogenesis of cystic fibrosis sinusitis. *Int Forum Allergy Rhinol* 2014; **4**: 132-137 [PMID: 24282147 DOI: 10.1002/alr.21252]

72 **Kang SH**, Piltcher OB, Dalcin Pde T. Sinonasal alterations in computed tomography scans in cystic fibrosis: a literature review of observational studies. *Int Forum Allergy Rhinol* 2014; **4**: 223-231 [PMID: 24415497 DOI: 10.1002/alr.21266]

73 **Keicho N**, Hijikata M. Genetic predisposition to diffuse panbronchiolitis. *Respirology* 2011; **16**: 581-588 [PMID: 21303426 DOI: 10.1111/j.1440-1843.2011.01946.x]

74 **Anthony M**, Singham S, Soans B, Tyler G. Diffuse panbronchiolitis: not just an Asian disease: Australian case series and review of the literature. *Biomed Imaging Interv J* 2009; **5**: e19 [PMID: 21610988 DOI: 10.2349/biij.5.4.e19]

75 **Poletti V**, Casoni G, Chilosi M, Zompatori M. Diffuse panbronchiolitis. *Eur Respir J* 2006; **28**: 862-871 [PMID: 17012632 DOI: 10.1183/09031936.06.00131805]

76 **Krishnan P**, Thachil R, Gillego V. Diffuse panbronchiolitis: a treatable sinobronchial disease in need of recognition in the United States. *Chest* 2002; **121**: 659-661 [PMID: 11834689 DOI: 10.1378/chest.121.2.659]

77 **Homma H**, Yamanaka A, Tanimoto S, Tamura M, Chijimatsu Y, Kira S, Izumi T. Diffuse panbronchiolitis. A disease of the transitional zone of the lung. *Chest* 1983; **83**: 63-69 [PMID: 6848335 DOI: 10.1378/chest.83.1.63]

78 **Fitzgerald JE**, King TE, Lynch DA, Tuder RM, Schwarz MI. Diffuse panbronchiolitis in the United States. *Am J Respir Crit Care Med* 1996; **154**: 497-503 [PMID: 8756828 DOI: 10.1164/ajrccm.154.2.8756828]

79 **Allen TC**. Pathology of small airways disease. *Arch Pathol Lab Med* 2010; **134**: 702-718 [PMID: 20441501 DOI: 10.1043/1543-2165-134.5.702]

80 **Tsang KWT.** Diffuse panbronchiolits: diagnosis and treatment. *Clin Pulm Med* 2000; **7**: 245-252

81 **Cervin A**, Wallwork B. Anti-inflammatory effects of macrolide antibiotics in the treatment of chronic rhinosinusitis. *Otolaryngol Clin North Am* 2005; **38**: 1339-1350 [PMID: 16326189 DOI: 10.1016/j.otc.2005.08.002]

82 **Harvey RJ**, Wallwork BD, Lund VJ. Anti-inflammatory effects of macrolides: applications in chronic rhinosinusitis. *Immunol Allergy Clin North Am* 2009; **29**: 689-703 [PMID: 19879444 DOI: 10.1016/j.iac.2009.07.006]

83 **Kudoh S**, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998; **157**: 1829-1832 [PMID: 9620913 DOI: 10.1164/ajrccm.157.6.9710075]

84 **Kanoh S**, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev* 2010; **23**: 590-615 [PMID: 20610825 DOI: 10.1128/CMR.00078-09]

85 **Cameron EJ**, McSharry C, Chaudhuri R, Farrow S, Thomson NC. Long-term macrolide treatment of chronic inflammatory airway diseases: risks, benefits and future developments. *Clin Exp Allergy* 2012; **42**: 1302-1312 [PMID: 22925316 DOI: 10.1111/j.13652222.2012.03979.x]

86 **Knowles MR**, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. *Am J Respir Crit Care Med* 2013; **188**: 913-922 [PMID: 23796196 DOI: 10.1164/rccm.201301-

0059CI]
87 **Loebinger MR**, Bilton D, Wilson R. Upper airway 2: Bronchiectasis, cystic fibrosis and sinusitis. *Thorax* 2009; **64**: 1096-1101 [PMID: 19952235 DOI: 10.1136/thx.2008.112870]
88 **Flight WG**, Jones AM. Cystic fibrosis, primary ciliary dyskinesia and non-cystic fibrosis bronchiectasis: update 2008-11. *Thorax* 2012; **67**: 645-649 [PMID: 21680564 DOI: 10.1136/thoraxjnl-2011-200467]
89 **Philpott CM**, McKiernan DC. Bronchiectasis and sino-nasal disease: a review. *J Laryngol Otol* 2008; **122**: 11-15 [PMID: 17592654]
90 **Sagel SD**, Davis SD, Campisi P, Dell SD. Update of respiratory tract disease in children with primary ciliary dyskinesia. *Proc Am Thorac Soc* 2011; **8**: 438-443 [PMID: 21926396 DOI: 10.1513/pats.201103-024SD]
91 **Leigh MW**, Pittman JE, Carson JL, Ferkol TW, Dell SD, Davis SD, Knowles MR, Zariwala MA. Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome. *Genet Med* 2009; **11**: 473-487 [PMID: 19606528 DOI: 10.1097/GIM.0b013e3181a53562]
92 **Mener DJ**, Lin SY, Ishman SL, Boss EF. 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**: 986-991 [PMID: 24124045 DOI: 10.1002/alr.21227]
93 **Min YG**, Shin JS, Choi SH, Chi JG, Yoon CJ. Primary ciliary dyskinesia: ultrastructural defects and clinical features. *Rhinology* 1995; **33**: 189-193 [PMID: 8919209]
94 **Drake-Lee AB**. Medical treatment of nasal polyps. *Rhinology* 1994; **32**: 1-4 [PMID: 8029616]
95 **Rollin M**, Seymour K, Hariri M, Harcourt J. Rhinosinusitis, symptomatology & amp; absence of polyposis in children with primary ciliary dyskinesia. *Rhinology* 2009; **47**: 75-78 [PMID: 19382500]
96 **Bush A**, Cole P, Hariri M, Mackay I, Phillips G, O'Callaghan C, Wilson R, Warner JO. Primary ciliary dyskinesia: diagnosis and standards of care. *Eur Respir J* 1998; **12**: 982-988 [PMID: 9817179 DOI: 10.1183/09031936.98.12040982]
97 **Campbell R**. Managing upper respiratory tract complications of primary ciliary dyskinesia in children. *Curr Opin Allergy Clin Immunol* 2012; **12**: 32-38 [PMID: 22157161 DOI: 10.1097/ACI.0b013e32834eccc6]
98 **Stillwell PC**, Wartchow EP, Sagel SD. Primary Ciliary Dyskinesia in Children: A Review for Pediatricians, Allergists, and Pediatric Pulmonologists. *Pediatr Allergy Immunol Pulmonol* 2011; **24**: 191-196 [PMID: 22276227 DOI: 10.1089/ped.2011.0099]
99 **Lucas JS,** Burgess A, Mitchison HM, Moya E, Williamson M, Hogg C; National PCD Service, UK.. Diagnosis and management of primary ciliary dyskinesia. *Arch Dis Child* 2014; **99**: 850-856 [PMID: 24771309 DOI: 10.1136/archdischild-2013-304831]
100 **Guilemany JM**, Angrill J, Alobid I, Centellas S, Prades E, Roca J, Pujols L, Bernal-Sprekelsen M, Picado C, Mullol J. United airways: the impact of chronic rhinosinusitis and nasal polyps in bronchiectasic patient's quality of life. *Allergy* 2009; **64**: 1524-1529 [PMID: 19772517 DOI: 10.1111/j.1398-9995.2009.02011.x]
101 **Chalmers JD**, Hill AT. Mechanisms of immune dysfunction and bacterial persistence in non-cystic fibrosis bronchiectasis. *Mol Immunol* 2013; **55**: 27-34 [PMID: 23088941 DOI: 10.1016/j.molimm.2012.09.011]
102 **Shirahata Y**. [Correlation between upper airway tract and lower airway tract in the break down of sinobronchiectasis]. *Nihon Jibiinkoka Gakkai Kaiho* 1990; **93**: 1991-1998 [PMID: 2292749]
103 **Shoemark A**, Ozerovitch L, Wilson R. Aetiology in adult patients with bronchiectasis. *Respir Med* 2007; **101**: 1163-1170 [PMID: 17223027 DOI: 10.1016/j.rmed.2006.11.008]
104 **Ramakrishnan VR**, Ferril GR, Suh JD, Woodson T, Green TJ, Kingdom TT. Upper and lower airways associations in patients with chronic rhinosinusitis and bronchiectasis. *Int Forum Allergy Rhinol* 2013; **3**: 921-927 [PMID: 23881553 DOI: 10.1002/alr.21204]
105 **Simon-Nobbe B**, Denk U, Pöll V, Rid R, Breitenbach M. The spectrum of fungal allergy. *Int Arch Allergy Immunol* 2008; **145**: 58-86 [PMID: 17709917 DOI: 10.1159/000107578]
106 **Knutsen AP**, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, Greenberger PA, Kariuki B, Kita H, Kurup VP, Moss RB, Niven RM, Pashley CH, Slavin RG, Vijay HM, Wardlaw AJ. Fungi and allergic lower respiratory tract diseases. *J Allergy Clin Immunol* 2012; **129**: 280-291; quiz 292-293 [PMID: 22284927 DOI: 10.1016/j.jaci.2011.12.970]
107 **Greenberger PA**. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002; **110**: 685-692 [PMID: 12417875 DOI: 10.1067/mai.2002.130179]
108 **Stevens DA**, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, Denning DW, Crameri R, Brody AS, Light M, Skov M, Maish W, Mastella G. Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* 2003; **37** Suppl 3: S225-S264 [PMID: 12975753 DOI: 10.1086/376525]
109 **Agarwal R**, Nath A, Aggarwal AN, Gupta D, Chakrabarti A. Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with acute severe asthma in a respiratory intensive care unit in North India. *Mycoses* 2010; **53**: 138-143 [PMID: 19207831 DOI: 10.1111/j.1439-0507.2008.01680.x]
110 **Agarwal R**. Allergic bronchopulmonary aspergillosis. *Chest* 2009; **135**: 805-826 [PMID: 19265090 DOI: 10.1378/chest.08-2586]
111 **Knutsen AP**, Bellone C, Kauffman H. Immunopathogenesis of allergic bronchopulmonary aspergillosis in cystic fibrosis. *J Cyst Fibros* 2002; **1**: 76-89 [PMID: 15463812 DOI: 10.1016/S1569-1993(02)00033-4]
112 **Chaudhary N**, Marr KA. Impact of Aspergillus fumigatus in allergic airway diseases. *Clin Transl Allergy* 2011; **1**: 4 [PMID: 22410255 DOI: 10.1186/2045-7022-1-4]
113 **Sudfeld CR**, Dasenbrook EC, Merz WG, Carroll KC, Boyle MP. Prevalence and risk factors for recovery of filamentous fungi in individuals with cystic fibrosis. *J Cyst Fibros* 2010; **9**: 110-116 [PMID: 20045384 DOI: 10.1016/j.jcf.2009.11.010]
114 **Kraemer R**, Deloséa N, Ballinari P, Gallati S, Crameri R. Effect of allergic bronchopulmonary aspergillosis on lung function in children with cystic fibrosis. *Am J Respir Crit Care Med* 2006; **174**: 1211-1220 [PMID: 16959918 DOI: 10.1164/rccm.200603-423OC]
115 **Wojnarowski C**, Eichler I, Gartner C, Götz M, Renner S, Koller DY, Frischer T. Sensitization to Aspergillus fumigatus and lung function in children with cystic fibrosis. *Am J Respir Crit Care Med* 1997; **155**: 1902-1907 [PMID: 9196093 DOI: 10.1164/ajrccm.155.6.9196093]
116 **Kanthan SK**, Bush A, Kemp M, Buchdahl R. Factors effecting impact of Aspergillus fumigatus sensitization in cystic fibrosis. *Pediatr Pulmonol* 2007; **42**: 785-793 [PMID: 17659599 DOI: 10.1002/ppul.20656]
117 **Schubert MS**. Allergic fungal sinusitis: pathophysiology, diagnosis and management. *Med Mycol* 2009; **47** Suppl 1: S324-S330 [PMID: 19330659 DOI: 10.1080/13693780802314809]
118 **deShazo RD**, Swain RE. Diagnostic criteria for allergic fungal sinusitis. *J Allergy Clin Immunol* 1995; **96**: 24-35 [PMID: 7622760 DOI: 10.1016/S0091-6749(95)70029-3]
119 **Gourley DS**, Whisman BA, Jorgensen NL, Martin ME, Reid MJ. Allergic Bipolaris sinusitis: clinical and immunopathologic characteristics. *J Allergy Clin Immunol* 1990; **85**: 583-591 [PMID: 2312993 DOI: 10.1016/0091-6749(90)90097-N]
120 **Schubert MS**. Allergic fungal sinusitis. *Clin Rev Allergy Immunol* 2006; **30**: 205-216 [PMID: 16785591 DOI: 10.1385/CRIAI: 30: 3: 205]
121 **Travis WD**, Kwon-Chung KJ, Kleiner DE, Geber A, Lawson W, Pass HI, Henderson D. Unusual aspects of allergic bronchopulmonary fungal disease: report of two cases due to Curvularia organisms associated with allergic fungal sinusitis. *Hum Pathol* 1991; **22**: 1240-1248 [PMID: 1748430 DOI: 10.1016/0046-8177(91)90106-Y]
122 **Shah A**, Panchal N, Agarwal AK. Concomitant allergic bronchopulmonary aspergillosis and allergic Aspergillus sinusitis: a review of an uncommon association*. *Clin Exp Allergy* 2001; **31**: 1896-1905 [PMID: 11737042 DOI: 10.1046/j.1365-2222.2001.01159.x]

123 **Leonard CT**, Berry GJ, Ruoss SJ. Nasal-pulmonary relations in allergic fungal sinusitis and allergic bronchopulmonary aspergillosis. *Clin Rev Allergy Immunol* 2001; **21**: 5-15 [PMID: 11471340 DOI: 10.1385/CRIAI: 21: 1: 5]
124 **Gan EC**, Thamboo A, Rudmik L, Hwang PH, Ferguson BJ, Javer AR. Medical management of allergic fungal rhinosinusitis following endoscopic sinus surgery: an evidence-based review and recommendations. *Int Forum Allergy Rhinol* 2014; **4**: 702-715 [PMID: 25044729 DOI: 10.1002/alr.21352]
125 **Kariya S,** Okano M, Nishizaki K. An Association Between Upper and Lower Respiratory Tract Diseases. *Ann Otolaryngol Rhinol* 2014; **1**: 1001

P- Reviewer: Berlucchi M, El-Shazly A, Noussios G
S- Editor: Song XX **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com