Commentary

Asthma exacerbation related to viral infections: An up to date summary

Mehdi Adeli[1,2,3], Tamara El-Shareif[2], Mohamed A. Hendaus[1,2,3]

[1]Department of Pediatrics, Section of Academic General Pediatrics, Sidra Medicine, [2]Department of Pediatrics, Hamad General Corporation, [3]Department of Clinical Pediatrics, Weill- Cornell Medicine, Doha, Qatar

Abstract

Asthma exacerbation can be a major life threatening event. Viruses have been pinned as the cause behind the vast majority of these exacerbations. The purpose of this short review is to explore the mechanisms behind these exacerbations, focusing mostly on viral infections as triggers. We will also be discussing the phenotypes prone to asthma exacerbation, the pathophysiology of viral induced asthma and ventilation patterns of asthmatic lungs. This manuscript will assist primary care physicians in delineating the proper pathophysiology of the disease as well as the management.

Keywords: Asthma, exacerbations, pulmonary function, virus-induced asthma

Introduction

Asthma is considered as one of the most common chronic diseases.[1] Its global prevalence reaches up to 334 million people.[2] Being a longstanding disease, it constitutes a high burden on patients, families, and health systems. In the United States alone, there are over 15 million annual clinic visits, and 2 million Emergency Room (ER) visits related to asthma. In addition to this, there are more than 500,000 yearly hospitalizations for severe asthma exacerbations.[3]

Asthma exacerbation is defined as a respiratory attack that requires emergency treatment, hospitalization or treatment with systemic corticosteroids.[4] Moreover, in terms of pulmonary function tests, an asthma exacerbation is defined as a reduction in forced expiratory volume (FEV1) of more than 20% from baseline, or a decrease in peak expiratory flow of >30% from baseline for 2 consecutive days at any time during the period of treatment.[4] In addition, asthma exacerbations might lead to accelerated decline in pulmonary function.[5-9]

On top of the financial burden,[10,11] asthma exacerbations can lead to a reduction in the patient's work or school attendance,[12-14] as well as an increase in mortality.[15]

Asthma-related deaths may not seem as striking as other diseases and often do not make headlines. However, according to the World Health Organization (WHO) report on chronic illnesses, there are approximately 250,000 avoidable deaths related to asthma.[16]

The most prominent trigger of asthma exacerbations is viral respiratory tract illness.[3,17] This review will further discuss viral infection in relation to asthma, and how rhinovirus (RV) can be the most causative viral agent responsible for predisposing asthma exacerbations in children and adults.[17-21]

Asthma exacerbations are preceded by about 7-10 days of airflow reduction and gradual increase in symptoms. This process continues till the symptoms become very notable, resulting in

Address for correspondence: Dr. Mehdi Adeli, Department of Pediatrics, Sidra Medicine, Doha - 26999, Qatar.
E-mail: madeli@sidra.org

Received: 31-01-2019 **Revised:** 01-02-2019 **Accepted:** 27-08-2019

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_86_19

How to cite this article: Adeli M, El-Shareif T, Hendaus MA. Asthma exacerbation related to viral infections: An up to date summary. J Family Med Prim Care 2019;8:2753-9.

the administration of corticosteroids, after which improvement follows a few days later.[22]

Exacerbation Prone Asthma

Exacerbation prone phenotypes

Exacerbation prone phenotypes are individuals with intrinsic and extrinsic risk factors for asthma exacerbation. The main intrinsic factors that predispose for exacerbations are deficiencies in the production of epithelial cell antiviral interferons type I (IFN-β and INFλ). On the other hand, extrinsic factors are more numerous and comprise of tobacco smoke, non-compliance to treatment, psychological factors, and preexisting comorbidities such as gastroesophageal reflux disease (GERD), obesity, rhinosinusitis, and non-steroidal anti-inflammatory drug (NSAID) intolerance.[3,23]

Factors behind exacerbation prone asthma

Exacerbations tend to happen in some patients more than others, making them "exacerbation prone". There are various factors which are known to contribute to the occurrence and frequency of asthma exacerbations. One of the culprits is race, a non-modifiable contributing factor. Exacerbation percentages rise amongst both African Americans and Hispanics compared to Caucasians.[3,24] Another factor is patient's poor access to health care, resulting in reliance on crisis management rather than regular visits. Moreover, deficiency in knowledge and education about the disease, results in decrease compliance to medications.[14,25-27] Similarly, poorly controlled patients suffered greater exacerbations when they have superimposing respiratory tract infections compared to well-controlled asthmatics.[25-28]

Further factors include chronic sinusitis,[29] uncontrolled eosinophilic inflammation,[30] and sensitivity to aeroallergens such as animal dander and house dust mites.[3,31] Factors such as tobacco smoke, the strongest modifiable risk factor[32] which increases airway neutrophils,[3,33] results in a higher prevalence of emergency visits and admissions.[32,34] Other factors are GERD and high body mass index (BMI).[29] The latter is linked to chemokine and pro-inflammatory factors,[35] including eotaxin, an eosinophil chemoattractant.[35,36]

Denlinger *et al.*[29] investigated the clinical, physiologic, inflammatory, and comorbidity factors associated with asthma exacerbation prone cases. The study that included 709 subjects in the Severe Asthma Research Program cohort (SARP)-3, investigated multiple factors that can predispose asthmatic patients to exacerbations such as such as race, sex, age, socioeconomic status, BMI, maximum post- albuterol reversibility, IgE, serum eosinophils, and comorbidities such as sinusitis, and GERD.[29,37] The study concluded that GERD, high BMI, and blood eosinophils were the three most common risk factors related to exacerbation, with a linear proportional relationship. The study also concluded that high eosinophils were associated with more vulnerable airways in adults but not in children.

The Relationship Between Respiratory Tract Infections and Asthma

The relationship between respiratory tract infections and the common cold was initially mentioned in the 12th century and remains valid till this day.[38]

Up to 60-70% of asthma exacerbations are associated with viral infections.[17] Multiple studies confirm that RV is the most common causative agent, and the most detected attributable factor in the 5 days preceding an asthma exacerbation.[39,40] Other viruses that cause asthma exacerbation are enterovirus, respiratory syncytial virus (RSV) type A and B, bocavirus, parainfluenza 3 virus, adenovirus, and many more.[41,42]

Seasonal Variation of Asthma Exacerbations

There are seasonal variations in hospital admission rates for asthma based on the seasonal viral upper respiratory infections.[43-46] The highest rate of exacerbations is in the fall season (28.8%), followed by spring (19.6%), winter (15.9%), and summer (14.5%).[45] Similarly asthma pediatric hospitalizations in a big city had a noticeable consecutive repetitive annual peak in September, specifically 7-10 days after school resumption, with a small peak in spring, which reinforces the same idea.[46]

Denlinger *et al.*[40] assessed the respiratory viral load and strain in a high-risk asthma cohort during a natural cold. The study discovered that patients are more prone to develop exacerbations if their secretions were still virus positive. Exacerbations were higher among RV-infected patients who had a high sputum neutrophil count. The same study noted that viral recovery from the lower airways as opposed to the upper airways indicates a greater risk of exacerbation.

Altered Immunity and Its Relation to Viral Induced Asthma Exacerbations

Patients with an altered immune response are at higher risk of experiencing exacerbations, namely those who have decreased cytokines; such as type I interferons (IFN-α, IFN-β) and type III interferons (IFN-λ).[3,47-49] IFNβ was found to be particularly deficient in asthmatic patients compared to others,[49] while IFN-λ was found imperative in the pathogenesis of exacerbations and the clinical outcome of RV infection in asthmatics.[50] Similarly, patients who display a greater T-helper cells-2 (TH_2) to T-helper cells-1 (TH_1) ratio are more at risk.[49-51] The production of TH_1 response is important for the limitation of the infection; hence a failure in the generation of such a response increases the chance of a viral induced exacerbation.[50]

Another risk factors include defective eosinophilic inflammation in response to upper respiratory tract infection, whether the defect was induced by viral infection or by uncheckable host inflammation.[49-51] Moreover, induction of apoptosis in virus infected epithelial cell in asthmatic patients is significantly less than in the normal population,[49,50] keeping in mind that IFN-β

is responsible for this apoptosis. Therefore, it is assumed that the decrease of the activating antiviral cytokines is the reason behind this unchecked immune response.[49,50]

In terms of antibodies, increased level of specific IgE to house dust mites in asthmatic patients may make asthmatic patients more vulnerable to exacerbations.[31,52,53] House dust mites may increase the level of specific IgE in asthmatic patients and result in a wheezy chest, which then can increase the probability of an exacerbation.[29,53] In a study conducted by Soto-Quiros *et al.*,[53] it was found that patients who have higher IgE antibodies to *D. pteronyssinus* and positive RV required more treatment for acute wheezing, compared to those who had lesser IgE titers.[53] This could be an evidence that there is an accentuated relationship between viral infections and wheezing in patients who have a higher sensitivity to house dust mites.[29]

How are Asthma Exacerbations Caused by Viral Infection?

Viral infections cause exacerbations via multiple mechanisms which include: The enhanced responsiveness of the respiratory tract, the increased eosinophilic inflammation of the airway, the enhanced lower airway neutrophilic inflammation, and the direct lower airway infection.[47,54-69] Asthma exacerbation was described by Szefler[70] as a volcano explosion from accumulation of airflow obstruction, hyper-responsiveness and inflammation that results from vial respiratory tract infections.

Respiratory tract enhanced responsiveness

Then literature has shown that that there is a strong enhanced responsiveness to allergens post viral infections. A decrease in FEV1 occur in 1/10 patients who are exposed to allergen alone. However, the same FEV1 can affect 8 in 10 patients if they were exposed to a combination of an allergen and RV.[54]

Akbarshahi *et al.*[31] investigated if house dust mites (HDM) impairs antiviral signaling, potentiating viral-induced asthma exacerbation. The study was conducted *in vitro* in human bronchial epithelial cells (HBECs) and in mice, by using sequential challenges with HDM and a viral infection mimic, Poly (I:C). It was noticed that the exposure to both a RV infection and HDM in sensitive mice compared to the exposure to the virus alone, resulted in a decrease in multiple immune pathway components such as IFN- λ, IFN-β, TLR3. The study also showed that host bronchial epithelial cells exposed to HDM showed a reduced antiviral response. The study concluded that the allergen effect on pattern recognition receptors (PRR) can present as a possible mechanism for flawed antiviral response, further potentiating exacerbations.[31]

Increased eosinophilic inflammation of the airway

Eosinophils have shown to be involved in airway remodeling through the production of growth factors and cytokines.[55-57] In the airway, smooth muscles produce eotaxin which is a chemoattractant for eosinophils.[58,59] Eotaxin is upregulated in asthma, and eosinophils in asthmatic patients display an enhanced response to eotaxin compared to non-asthmatics.[60] In a study conducted in 2018, it was found that remodeling in medium to large sized airways in patients with severe asthma is directly associated with systemic eosinophilic inflammation.[61] This is important because remodeling is the essential feature of asthma and exacerbations.[58] Moreover, RV pathogenesis in asthma occurs through eosinophilic inflammatory response resulting from the induction of the epithelial-derived cytokines thymic stromal lymphopoietin (TSLP), IL_{25} and IL_{33}. These mediators stimulate production of IL_5 that is responsible for eosinophilic infiltration.[62] Furthermore, and during an acute viral infection stage, patients have a greater influx and recruitment of eosinophils when compared to the pre-infection period.[63]

Enhanced lower airway neutrophilic inflammation

Rhinovirus infection can increases the level of neutrophils. Zhu *et al.*[64] noted a positive association between rhinovirus load and each of the following CD_{45}^+, CD_{68}^+, and CD_{20}^+ till 4 days after the acute infection. The authors concluded that there is an association between the level of neutrophils and a 10% decrease in FEV_1.

Similarly, Jarjour *et al.*,[65] investigated if RV infections generate nasal proinflammatory mediators which contributed to development of neutrophilic airway inflammation. The study was conducted through experimental Rhinovirus16 nasal inoculation exposure in known allergic asthmatic patients. The participants has had a higher neutrophil value in bronchoalveolar lavage fluid from lower respiratory airways 96 hours after the initial infection when compared to baseline titer value.[40,65]

Moreover, patients who have a higher neutrophil load in their sputum have a higher risk of asthma exacerbations.[66,67] This neutrophilic inflammation is also related to the induction of different chemokines and cytokines in the upper airway, which could also be recovered from the blood. Additionally, Granulocyte colony-stimulating factor (G-CSF) and nasal IL-8 were also augmented in relation to the neutrophil recruitment available in patients' bronchoalveolar lavage.[65] The rise in IL-8 can be related to the intensity and severity of symptoms.[68]

Direct lower respiratory tract infection

Direct viral infection of the lower airway increases the chances of exacerbations. Mosser *et al.*[69] conducted a study on 19 subjects after an experimental RV16 infection. Patients underwent immune-histochemical staining of bronchial biopsies before an infection with RV16, and during the acute infection. Some biopsies were negative for RV when the immediately adjacent samples were positive, indicating that there is a regional patchy distribution of the virus during infection, and that there is a direct viral airway infection process which can predispose to exacerbations.[69]

Ventilation Patterns in Asthmatic Lungs

In well-controlled asthma, there are baseline ventilation defects not found in a normal lungs.[71,72] However, it is not well known yet of where chronic airway obstruction in asthmatic patient, recurrent infections, or poorly controlled forms of the disease are the culprit for permanent ventilation defects, and a predisposition for acute exacerbations.[3] Zha *et al.*[71] investigated lobar ventilation patterns within asthmatic lungs using ^{3}He magnetic resonance imaging (HP ^{3}He MRI). The study included 82 subjects with different asthma severity scores (20 severe, 48 mild to moderate, and 14 non-asthmatics). The participants underwent pulmonary function testing, computed tomography (CT) and HP ^{3}He MRI. The lungs were segmented into 5 lobes, and ventilation defect percent (VDP), was classified into low ventilation percent, medium ventilation percent, and high ventilation percent. The study noticed a pattern of strength between ventilation defects and the severity of asthma. The study concluded greater ventilation abnormalities have a linear proportion with the severity of asthma.[71]

Asthma Exacerbation Predictors

Patients with 2 or more asthma attacks and those who had recent steroid treatment bursts, were also found to be at a higher risk.[73,74] Overall, any recent exacerbation will mostly result in a repeat of similar future attacks, regardless of severity classification. Therefore physicians should be aware of the patients' exacerbation history in order to better create a management plan.[73] Miller *et al.*[73] analyzed the (TENOR) study database in 2007, finding a 5-6 fold increase in future severe asthma with a positive history of recent severe asthma. Patients classified with severe asthma, had double the chance of experiencing a future exacerbation when compared with patients with moderate asthma.

Prevention of Asthma Exacerbations

Asthma exacerbations can result from genetic predispositions, comorbidities, lack of patient adherence to comorbidity treatment plan and much more.[75,76] Therefore the initial step to treat asthma and prevent asthmatic exacerbation is to identify these common modifiable risk factors.[76] Each asthmatic patient needs to be systematically assessed. Those with severe asthma require more care, preferably via a multidisciplinary approach to differentiate patients who are suffering from severe refractory asthma and patients who have poor symptom control caused by their co-morbidities.[75]

Studies showed that the most effective method to prevent severe exacerbations is the combined maintenance therapy of inhaled corticosteroids (ICS) and long acting Beta agonists (LABA) on a fixed daily dose basis. This combination was found to be superior to the isolated use of the low dose ICS in reducing asthmatic exacerbations.[77]

The heterogeneity of RV serotypes is an obstacles in finding an effective antiviral therapy or potential vaccine to prevent asthma exacerbation triggered by such common virus.[78]

Due to seasonal variation of exacerbations, with the highest incidence rate occurring in the fall season, it was found that a pre-seasonal treatment of Omalizumab 4-6 weeks prior to returning to school, significantly lowered the incidence rate of exacerbations. Additionally, Omalizumab improved patient IFN-a responses to rhinovirus.[79]

Non-pharmacologic treatment was also investigated to reduce exacerbation in severe asthmatic patients unresponsive to maximum medical treatment, and who had evidence of respiratory airway remodeling. In such patients, it was found that bronchial thermoplasty resulted in long term quality of life improvement, less healthcare utilization, and a decrease in exacerbations. Biopsy studies on patients who were treated with bronchial thermoplasty demonstrated disease modifying effects on the smooth muscles, the bronchial nerve endings and the inflammatory mediators. Thermoplasty is not a standalone treatment, but rather a complementary treatment to current guideline treatment for severe asthma and biologic modifier drug usage.[80]

Proper education and conversations with the patient should always be a priority in the management plan.The importance of this point lies in the fact that a lot of the clinical outcomes are highly dependent on factors such as inhaler technique, medication adherence and understanding the nature of the disease. Patients or their caretakers should have a self-management plan of the disease, as it can ultimately improve the control of the disease and reduce the exacerbation risk.[81,82]

Conclusions and Recommendations

Asthma is an exceedingly prevalent worldwide health issue, Asthma exacerbations are common and serious events that can be life threatening and are a financial burden on the individual and the community as a whole.

Some asthmatic patients are more prone than others to exacerbations. In addition intrinsic factors, potential extrinsic modifiable risk factors of exacerbations are eosinophilic inflammation, uncontrolled allergies, sinusitis, obesity, smoking, GERD and poor access to care. Moreover, GERD, high BMI and blood eosinophils are the three most common risk factors related to exacerbation.

Respiratory infections are the main culprits of asthma exacerbations, and rhinovirus being the most common agent. Viral infections cause exacerbations via multiple mechanisms which include the enhanced responsiveness of the respiratory tract, the increased eosinophilic inflammation of the airway, the enhanced lower airway neutrophilic inflammation, and the direct lower airway infection. Exacerbations may lead to expedited long term loss of lung function and ventilation defects.

Currently, there are no therapies that guarantee the prevention of asthma exacerbations. The most effective treatment plan

is a combination maintenance therapy of ICS and LABA. A seasonal dose of Omalizumab might reduce the number of exacerbations, if given 4-6 weeks in advance. Thermoplasty is another non-pharmacological treatment that can be successful in the management of severe asthma that is not responsive to the maximum medical treatment.

Future studies are recommended to further pursue this aspect of the disease with clinical trials that aim to find regimens that can successfully prevent exacerbations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Abbreviations: PEF, Peak Flow Meter; ILC2, Type 2 innate lymphoid cell; IFN-α, Interferon alpha; IFN-β, Interferon beta; INFλ, interferon Gama; EPA, Exacerbation Prone Asthma; FEV, Forced Expiratory Volume; IL5, Interleukin 5; IL25, Interleukin 25; IL32, Interleukin 32; RV16, Rhinovirus 16; GERD, Gastro-Esophageal Reflux Disease; BMI, Body Mass Index

References

1. Hendaus MA, Jomha FA, Alhammadi AH. Is ketamine a lifesaving agent in childhood acute severe asthma? Ther Clin Risk Manag 2016;12:273-9.
2. The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network, 2014. Available from: http://www.globalasthmanetwork.org/publications/Global_Asthma_Report_2014.pdf. [Last accessed on 2019 Jan 30].
3. Dougherty R, Fahy JV. Acute exacerbations of asthma: Epidemiology, biology and the exacerbation-prone phenotype. Clin Exp Allergy 2009;39:2:193-202.
4. Meltzer EO, Kuna P, Nolte H, Nayak AS, LaForce C, on behalf of the P04073 Study Investigators. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. Eur Respir J 2012;39:279e89.
5. Ortega H, Yancey SW, Keene ON, Gunsoy NB, Albers FC, Howarth PH. Asthma exacerbations associated with lung function decline in patients with severe eosinophilic asthma. J Allergy Clin Immunol Pract 2018:6:980-6.e1.
6. Matsunaga K, Hirano T, Oka A, Tanaka A, Kanai K, Kikuchi T, *et al.* Progression of irreversible airflow limitation in asthma: Correlation with severe exacerbations. J Allergy Clin Immunol 2015;3:759-64.
7. Matsunaga K, Ichikawa T, Oka A, Morishita Y, Kanai K, Hiramatsu M, *et al.* Changes in forced expiratory volume in 1 second overtime in patients with controlled asthma at baseline. Respir Med 2014;108:976-82.
8. Ortega H, Yancey SW, Keene ON, Gunsoy NB, Albers FC, Howarth PH. Asthma Exacerbations associated with lung function decline in patients with severe eosinophilic asthma. J Allergy Clin Immunol Pract 2017;219830004-7.
9. Hirano T, Matsunaga K. Late-onset asthma: Current perspectives. J Asthma Allergy 2013;11:19-27.
10. Taminskiene V, Alasevicius T, Valiulis A, Vaitkaitiene E, Stukas R, Hadjipanayis A, *et al.* Quality of life of the family of children with asthma is not related to asthma severity. Eur J Pediatr 2019178:369-76.
11. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol 2011;127:145-52.
12. Steinemann A, Wheeler AJ, Larcombe A. Fragranced consumer products: effects on asthmatic Australians. Air Qual Atmos Health. 2018;11:365-71. doi:10.1007/s11869-018-0560-x.
13. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol 2012;129:1229-35.
14. Pavord, ID, Mathieson N, Scowcroft A, Pedersini R, Isherwood G, Price D. The impact of poor asthma control among asthma patients treated with inhaled corticosteroids plus long-acting beta2-agonists in the United Kingdom: A cross-sectional analysis. NPJ Prim Care Respir Med 2017;27:17.
15. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: A systematic analysis for the global burden of disease study 2015. Lancet Respir Med 2017;5:691-706.
16. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. Geneva, Switzerland: World Health Organization; 2007. p. 15-6. Available from https://www.who.int/gard/publications/GARD%20Book%202007.pdf?ua=1. [Last accessed on 2019 Sep 28].
17. Hammond C, Kurten M, Kennedy JL. Rhinovirus and asthma: A storied history of incompatibility. Curr Allergy Asthma Rep 2015;15:502.
18. Kim WK, Gern JE. Updates in the relationship between human rhinovirus and asthma. Allergy Asthma Immunol Res 2012;4:116-21.
19. Robledo Aceves M, Barrón Balderas A, Jaime Ornelas ML. Most commonly isolated viruses in asthma exacerbation and their correlation with eosinophil and total serum immunoglobulin E levels. Arch Argent Pediatr 2018;116:192-7.
20. Wark PA, Johnston SL, Moric I, Simpson JL, Hensley MJ, Gibson PG. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. Eur Respir J 2002;19:68-75.
21. Grissell TV, Powell H, Shafren DR, Boyle MJ, Hensley MJ, Jones PD, *et al.* Interleukin-10 gene expression in acute virus-induced asthma. Am J Respir Crit Care Med 2005;172:433-9.
22. Tattersfield A, Postma, D, Barnes, P, Svensson K, Bauer CA, O'Byrne PM, *et al.* Exacerbations of asthma: A descriptive study of 425 severe exacerbations. The FACET international study group. Am J Respir Crit Care Med 1999:160:594-9.
23. Loymans RJ, Sterk PJ. Exacerbation-prone asthma: A separate bioclinical phenotype? Am J Respir Crit Care Med 2017;195:275-7.
24. Erickson SE, Iribarren C, Tolstykh IV, Blanc PD, Eisner MD. Effect of race on asthma management and outcomes in a large, integrated managed care organization. Arch Intern Med 2007;167:1846-52.
25. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM.

Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 1998;157:1804-9.

26. Boulet LP, Deschesnes F, Turcotte H, Gignac F. Near-fatal asthma: Clinical and physiologic features, perception of bronchoconstriction, and psychologic profile. J Allergy Clin Immunol 1991;88:838-46.
27. Alvarez GG, Schulzer M, Jung D, Fitzgerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. Can Respir J 2005;12:265-70.
28. Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B, Hansel NN, *et al.* Mortality in patients hospitalized for asthma exacerbations in the United States. Am J Respir Crit Care Med 2006;174:633-8.
29. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, *et al.* Inflammatory and co-morbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med 2017;195:302-13.
30. De Groot JC, Amelink M, de Nijs SB, Plaat R, Reitsma BH, Storm H, *et al.* Risk factors for frequent severe exacerbations in late-onset eosinophilic asthma. Am J Respir Crit Care Med 2015;192:899-902.
31. Akbarshahi H, Menzel M, Ramu S, Mahmutovic Persson I, Bjermer L, Uller L. House dust mite impairs antiviral response in asthma exacerbation models through its effects on TLR3. Allergy 2018;73:1053-63.
32. Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, *et al.* Assessing future need for acute care in adult asthmatics: The Profile of asthma risk study: A prospective health maintenance organization-based study. Chest 2007;132:1151-61.
33. Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163:1304-9.
34. Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA Jr. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. Chest 2003;123:1472-9.
35. Vasudevan AR, Wu H, Xydakis AM, Jones PH, Smith EO, Sweeney JF, *et al.* Eotaxin and obesity. J Clin Endocrinol Metab 2006;91:256-61.
36. Park SW, Kim DJ, Chang HS, Park SJ, Lee YM, Park JS, *et al.* Association of interleukin-5 and eotaxin with acute exacerbation of asthma. Int Arch Allergy Immunol 2003;131:283-90.
37. Severe Asthma Research Program (SARP). A National Institute of Health/National Heart, Lung and Blood Institute Sponsored Network. www.severeasthma.org.
38. Rosner F. Moses maimonides' treatise on asthma. Thorax 1981;36:245-51.
39. Gern JE. Viral and bacterial infections in the development and progression of asthma. J. Allergy Clin Immunol 2000;105:S497-502.
40. Denlinger LC, Sorkness RL, Lee WM, Evans MD, Wolff MJ, Mathur SK, *et al.* Lower airway rhinovirus burden and the seasonal risk of asthma exacerbation. Am J Respir Crit Care Med 2011;184:1007-14.
41. Arden KE, McErlean P, Nissen MD, Sloots TP, Mackay IM. Frequent detection of human rhinoviruses, paramyxoviruses, coronaviruses, and bocavirus during acute respiratory tract infections. J Med Virol 2006:78:1232-40.
42. Robledo Aceves M, Barrón Balderas A, Jaime Ornelas ML. Most commonly isolated viruses in asthma exacerbation and their correlation with eosinophil and total serum immunoglobulin E levels. Arch Argent Pediatr 2018:116 :192-7.
43. Venarske DL, Busse WW, Griffin MR, Gebretsadik T, Shintani AK, Minton PA, *et al.* The relationship of rhinovirus-associated asthma hospitalizations with inhaled corticosteroids and smoking. J Infect Dis 2006;193:1536-43.
44. DuBuske L, Newbold P, Wu Y, Trudo F. Seasonal variability of exacerbations of severe, uncontrolled eosinophilic asthma and clinical benefits of benralizumab. Allergy Asthma Proc 2018;39:345-9.
45. Teach SJ, Gergen PJ, Szefler SJ, Mitchell HE, Calatroni A, Wildfire J, *et al.* Seasonal risk factors for asthma exacerbations among Inner City Children. J Allergy Clin Immunol 2015;135:1465-73.
46. Johnston NW, Johnston SL, Duncan JM, Greene JM, Kebadze T, Keith PK, *et al.* The september epidemic of asthma exacerbations in children: A search for etiology. J Allergy Clin Immunol 2005;115:132-8.
47. Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, *et al.* Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. J Allergy Clin Immunol 2012;130:489-95.
48. Jackson DJ, Gern JE, Lemanske RF. The contributions of allergic sensitization and respiratory pathogens to asthma inception. J Allergy Clin Immunol 2016;137:659-65.
49. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, *et al.* Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005;201:937-47.
50. Message SD, Laza-Stanca V, Mallia P, Parker HL, Zhu J, Kebadze T, *et al.* Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. Proc Natl Acad Sci USA 2008;105:13562-7.
51. Gill MA, Bajwa G, George TA, Dong CC, Dougherty II, Jiang N, *et al.* Counterregulation between the FceRI pathway and antiviral responses in human plasmacytoid dendritic cells. J Immunol 2010;184:5999-6006.
52. Kim HH, Yoon J-S, Chun YH, Choi SJ, Kim HS, Won S, *et al.* House dust mite sensitization as a risk factor for exacerbation of asthma in the fall. Am J Respir Crit Care Med 193;2016:A1412.
53. Soto-Quiros M, Avila L, Platts-Mills TA, Hunt JF, Erdman DD, Carper H, *et al.* High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. J Allergy Clin Immunol 2012:129:1499-505.
54. Lemanske RF, Dick EC, Swenson CA, Vrtis RF, Busse WW. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest 1989;83:1-10.
55. Broekema M, Volbeda F, Timens W, Dijkstra A, Lee NA, Lee JJ, *et al.* Airway eosinophilia in remission and progression of asthma: Accumulation with a fast decline of FEV (1). Respir Med 2010;104:1254-62.
56. Yang YC, Zhang N, Van Crombruggen K, Hu H, Hong SL, Bachert C. Transforming growth factor-beta1 in inflammatory airway disease: A key for understanding inflammation and remodeling. Allergy 2012;67:1193-202.
57. Humbles A, Clare ML, McMillan JS, Friend SD, Xanthou G,

McKenna EE, *et al.* A critical role for eosinophils in allergic airways remodeling. Science 2004;17:1776-9.

58. Doeing DC, Solway J. Airway smooth muscle in the pathophysiology and treatment of asthma. J Appl Physiol (1985) 2013;114:834-43.
59. Pease JE, Williams TJ. Eotaxin and asthma. Curr Opin in Pharmacol 2001;1:248-53.
60. Sannohe S, Adachi T, Hamada K, Honda K, Yamada Y, Saito N, *et al.* Upregulated response to chemokines in oxidative metabolism of eosinophils in asthma and allergic rhinitis. Eur Respir J 2003;21:925-31.
61. Kim S, Nam Jin K, Cho SH, Kang HR. Severe asthma phenotypes classified by site of airway involvement and remodeling via chest CT scan. J Investig Allergol Clin Immunol 2018;28:312-20.
62. Ritchie AI, Jackson DJ, Edwards MR, Johnston SL. Airway epithelial orchestration of innate immune function in response to virus infection. A focus on asthma. Ann Am Thorac Soc 2016;13:S55-63.
63. Calhoun WJ, Dick EC, Schwartz LB, Busse WW. A common cold virus, rhinovirus 16, potentiates airway inflammation after segmental antigen bronchoprovocation in allergic subjects. J Clin Invest 1994;94:2200-8.
64. Zhu J, Message SD, Qiu Y, Mallia P, Kebadze T, Contoli M, *et al.* Airway inflammation and illness severity in response to experimental rhinovirus infection in asthma. Chest 2014;145:1219-29.
65. Jarjour N, Gern JE, Kelly EA, Swenson CA, Dick CR, Busse WW. The effect of an experimental rhinovirus 16 infection on bronchial lavage neutrophils. J Allergy Clin Immunol 2000;105:1169-77.
66. Ordonez CL, Shaughnessy TE, Matthay MA, Fahy JV. Increased neutrophil numbers and IL-8 levels in airway secretions in acute severe asthma: Clinical and biologic significance. Am J Respir Crit Care Med 2000;161:1185-90.
67. Lamblin C, Gosset P, Tillie-Leblond I, Saulnier F, Marquette CH, Wallaert B, *et al.* Bronchial neutrophilia in patients with noninfectious status asthmaticus. Am J Respir Crit Care Med 1998;157:394-402.
68. Fleming HE, Little FF, Schnurr D, Avila PC, Wong H, Liu J, *et al.* Rhinovirus-16 colds in healthy and in asthmatic subjects: Similar changes in upper and lower airways. Am J Respir Crit Care Med 1999;160:100-8.
69. Mosser AG, Vrtis R, Burchell L, Lee WM, Dick CR, Weisshaar E, *et al.* Quantitative and qualitative analysis of rhinovirus infection in bronchial tissues. Am J Respir Crit Care Med 2005;171:645-51.
70. Szefler S. Asthma exacerbations: Putting a lid on the volcano. J Allergy Clin Immunol 2008;122:697-9.
71. Zha W, Kruger SJ, Cadman RV, Mummy DG, Evans MD, Nagle SK, *et al.* Regional heterogeneity of lobar ventilation in asthma using hyperpolarized helium-3 MRI. Acad Radiol 2018;25:169-78.
72. Mummy DG, Kruger SJ, Zha W, Sorkness RL, Jarjour NN, Schiebler ML, *et al.* Ventilation defect percent in helium-3 magnetic resonance imaging as a biomarker of severe outcomes in asthma. J Allergy Clin Immunol 2018;141:1140-41.e4.
73. Miller MK, Lee JH, Miller DP, Wenzel SE. Recent asthma exacerbations: a key predictor of future exacerbations. Respir Med 2007;101:481-9.
74. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, *et al.* Design and baseline characteristics of the epidemiology and natural history of asthma: Outcomes and treatment regimens (TENOR) study: A large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2004;92:32-9.
75. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: Clinical impact and management. Respirology 2017;22:651-61.
76. Feldman AS, He Y, Moore ML, Hershenson MB, Hartert TV. Toward primary prevention of asthma. Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma. Am J Respir Crit Care Med. 2015;191:34-44.
77. Loymans RJ, Gemperli A, Cohen J, Rubinstein SM, Sterk PJ, Reddel HK, *et al.* Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: Network meta-analysis. BMJ 2014;348:3009.
78. Privolizzi R, Solari R, Johnston SL, McLean GR. The application of prophylactic antibodies for rhinovirus infections. Antivir Chem Chemother 2014;23:173-7.
79. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, *et al.* Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J Allergy Clin Immunol 2015;136:1476-85.
80. Hall C, Nici L, Sood S, ZuWallack R, Castro M. Nonpharmacologic therapy for severe persistent asthma. J Allergy Clin Immunol Pract 2017;5:928-35.
81. Graham LM, Eid N. The impact of asthma exacerbations and preventive strategies. Curr Med Res Opin 2015;31:825-35.
82. Chang YS. Non-pharmacologic Therapies for Severe Asthma. Severe Asthma. Singapore: Springer; 2018. p. 123-9.