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

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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.[5,6,7,8,9]

On top of the financial burden,[10,11] asthma exacerbations can lead to a reduction in the patient's work or school attendance,[12,13,14] 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.[17,18,19,20,21]

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 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 INF λ). 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.[14,25,26,27] Similarly, poorly controlled patients suffered greater exacerbations when they have superimposing respiratory tract infections compared to well-controlled asthmatics.[25,26,27,28]

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 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.[43,44,45,46] 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). [3,47,48,49] IFN β 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 (TH₂) to T-helper cells-1 (TH₁) ratio are more at risk.[49,50,51] The production of TH₁ 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. [49,50,51] 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.

[47,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69] Asthma exacerbation was described by Szeffler[70] as a volcano explosion from accumulation of airflow obstruction, hyper-responsiveness and inflammation that results from viral respiratory tract infections.

Respiratory tract enhanced responsiveness

Then literature has shown 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.[55,56,57] 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), IL₂₅ and IL₃₃. These mediators stimulate production of IL₅ 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 increase the level of neutrophils. Zhu *et al.*[64] noted a positive association between rhinovirus load and each of the following CD₄₅⁺, CD₆₈⁺, and CD₂₀⁺ 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 FEV₁.

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 have 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 immunohistochemical 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 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 ^3He magnetic resonance imaging (HP ^3He 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 ^3He 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- α 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.

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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; IFN γ , interferon Gama; EPA, Exacerbation Prone Asthma; FEV₁, Forced Expiratory Volume; IL5, Interleukin 5; IL25, Interleukin 25; IL32, Interleukin 32; RV16, Rhinovirus 16; GERD, Gastro-Esophageal Reflux Disease; BMI, Body Mass Index

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