REVIEW ARTICLE

Virus and Asthma

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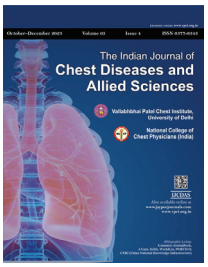

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Abstract

Asthma is an inflammatory disease of the airways that affects more than 300 million people around the world. In both children and adults, viral respiratory infections are the most common cause of asthma exacerbations. In bronchial asthma, respiratory viral infection involves several issues: (1) Respiratory virus infection in infancy is associated with asthma later in life; (2) Respiratory virus infection is associated with acute exacerbations of bronchial asthma; and, (3) Glucocorticosteroids (GC) are ineffective for controlling asthma-related symptoms. The purpose of this review is to provide a comprehensive overview of the role of viruses in asthma exacerbations, as well as the main inflammatory cells, mediators, and molecular pathways involved in asthma immune responses. Additionally, it highlights novel therapeutic targets for managing virus-induced asthma based on current clinical and epidemiological research.

Keywords: Asthma, Exacerbation, Therapeutics, Viruses.

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Abbreviations used in this Article

ABG = Arterial blood gas; ABPA = Allergic broncho pulmonary aspergillosis; ACE = Angiotensin converting enzyme; BEC = Bronchial epithelial cells; FEV = Forced expiratory volume; FEV1 = Forced expiratory volume in 1 second; HA = Hemagglutinin; HDM = Human dust mite; HRV = Human rhinovirus; ICS = Inhaled corticosteroid; IFN = Interferon; Ig E = Immunoglobulin E; Ig G = Immunoglobulin G; IL = Interleukin; LABA = Long-acting beta agonist; MERS = Middle east respiratory syndrome; PEF = Peak expiratory flow; PEFR = Peak expiratory flow rate; RSV = Respiratory syncytial virus; RTPCR = Reverse transcriptase polymerase chain reaction; SABA = short acting beta agonist; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; TLR = Toll like receptor; TMPRSS 2 = Transmembrane protease serine 2; TSLP = Thymic stromal lymphopoietin.

Introduction

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. The history of respiratory symptoms, such as wheezing, chest tightness, shortness of breath, and cough, that fluctuate over time and in intensity, together with changeable airflow restriction, serve as its defining characteristics.[1] Children of all ages with wheezing disorders and asthma, as well as adults experiencing an exacerbation, are all directly linked to viral respiratory infections. There is growing concern about how viral infections of the upper respiratory tract may contribute to asthma development because they are one of the main causes.[2] Viral infections produce common cold symptoms and cause acute inflammatory rhinitis. They may also play a role in asthma development and potentially, airway remodeling through increased inflammation of the lower airways.[3] In this review, we give a general background of the role of viruses in the processes of asthma exacerbation and asthma induction as well as focus on clinical, and epidemiologic investigations and new therapeutic targets for virus-induced exacerbations of asthma.

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Incidence and Prevalence of Coinfection

Asthma affects more than 241 million people worldwide, which makes it one of the most prevalent chronic respiratory diseases, with a high morbidity and mortality rate.[4] Asthma prevalence, severity, and death seem to be very geographically variable. The highest rates of asthma-related death are seen in low and middle-income countries, even though high-income countries have a larger incidence of asthma.[5]

Children and adults have different patterns for the incidence and prevalence of asthma, which typically first manifests in childhood but can happen at any point in life. In the late-onset phenotype of asthma, we can see adults developing asthma later in life with no previous history of childhood asthma.[6] Boys have a greater incidence and prevalence compared to girls in the prepubertal age group. Later, this pattern changes as both males and females are equally affected with slight female predominance.[4] Several respiratory viral pathogens

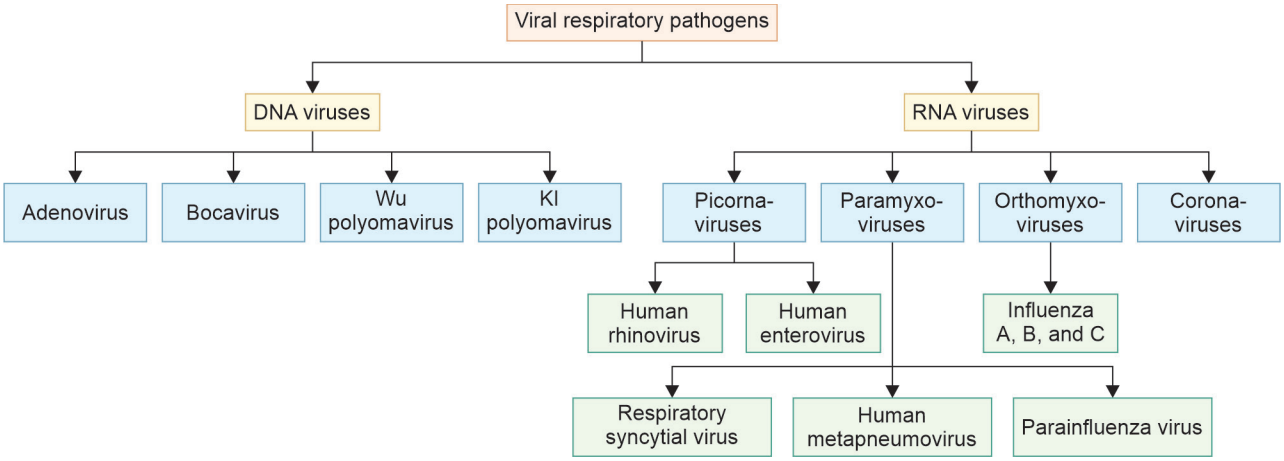

Fig. 1: Respiratory viral pathogens associated with asthma exacerbations

can cause asthma exacerbations (Fig. 1).[7] The common etiologies for viral bronchiolitis are *respiratory syncytial virus (RSV), rhinovirus, boca virus, human metapneumovirus*, followed by less common ones *adenovirus, influenza, parainfluenza, and coronavirus*. More than 80% of acute exacerbations in children are caused by respiratory viruses, and 60–70% of these exacerbations are frequently caused by the *human rhinovirus (HRV)*, which also causes the common cold. The most common cause of acute asthma exacerbations in both children and adults is the *HRV*.[7–13] The role of respiratory viral infections is discussed in Table 1.

Pathophysiology

Individual's genetics and environment play an important role in asthma exacerbation, and viral infections are common triggers of asthma exacerbation.[14,15] Lower respiratory tract infections caused by respiratory viruses lead to wheezing episodes, which subsequently lead to the development of asthma in childhood.[16–18] Interestingly, different viruses use different pathways to trigger airway inflammation. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invades the human host through the nose, travels to the lower respiratory tract, and binds to the Angiotensin converting enzyme 2 (ACE2) receptor on the alveolar cells by the proteolytic activity of transmembrane protease serine 2 (TMPRSS2), which triggers several pro-inflammatory cytokines, including interleukin-6 (IL-6), which can aggravate asthma.[19–21] *Influenza viruses*, one of the leading causes of pneumonia or bronchitis in childhood, enter the lower respiratory tract and bind to sialic acid on the epithelial cells of alveoli, and endocytosis occurs through the hemagglutinin (HA) component. Later, the virus multiplies inside the cell and hijacks the host machinery, which induces immune responses, of which prolonged presence of IL-13 can lead to asthma exacerbation.[22–24] RSV is a negative-stranded RNA virus that binds to CXCR3 on the surface of respiratory mucosal cells, which initiates viral envelope fusion and internalization. RSVs enter the smaller airways and spread to the deeper parts of the lung, leading to apoptosis of epithelial cells, mucus hypersecretion, airway obstruction, and wheezing.[25–27] *Rhinovirus* is a positive non-enveloped strand RNA virus that causes a common cold in children and increased exacerbations in asthmatics. The RV enters the host and binds to the mucosal epithelial receptors. Subsequently, the viral capsid binds to toll like receptor-4 (TLR-4) innate receptors, leading to the activation of innate immune responses such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). The release of these alarmins initiates the cascade activation of inflammatory cells, which induces epithelial permeability, loss of epithelial barrier integrity, release of host DNA, and further entry of viral proteins, leading to impaired lung function, airway obstruction, and airway hyper-responsiveness (Fig. 2).[28–30] The viruses bind to respective receptors in surface epithelial cells and activate downstream pathways.[30] Viral infections can cause asthma to develop and aggravate in asthma sufferers through the following mechanisms: (1) Enhanced receptiveness of the airways, (2) Augmented eosinophilic inflammation, (3) Heightened neutrophilic inflammation of the airway, (4) The direct infection of the lower airway.

Enhanced Receptiveness of the Airways

The respiratory tract is more sensitive following viral infection. It was observed that multiple immune pathway elements, including IFN-λ, IFN-β, and TLR3, decreased when sensitive mice were subjected to an RV infection with human dust mite (HDM), as opposed to simply the virus alone. The study also showed that host bronchial epithelial cells (BEC) exposed to HDM had a reduced antiviral response.[31]

Inoculating 14 people with mild disease with either RV16 or a placebo, Cheung et al.[32] reported that airway responsiveness momentarily increased during the acute infection and recovered to baseline levels by 1 week after the inoculation. Airway responsiveness to inhaled methacholine was significantly higher during the acute RV16 infection and remained raised for as long as 15 days after the infection, in contrast to changes in airway responsiveness. This reinforces the theory that viral infections may increase the airway's responsiveness to triggers that cause bronchoconstriction in people with asthma.

Augmented Eosinophilic Inflammation

Viral infection results in an increase in eosinophil count in the airway epithelium of people with allergic asthma, and high levels of eosinophilic cationic protein are found in the sputum of asthmatic patients with viral infection. Hence, during or after a viral infection, eosinophils are attracted to and activated in asthmatic airways.[33]

Due to their ability to produce cytokines and growth factors, eosinophils have been found to have a role in the remodeling of the airways. Thymic stromal lymphopoietin, IL-25, and IL-33 are examples of proinflammatory cytokines and chemokines that are released because of cytopathic damage to the airway epithelium caused by viral infection.

Table 1: Overview of study characteristics associated with respiratory viral infections

S.no	*Author*	*Study design*	*Age group*	*Virus detection method*	*Results*
1	Merckx et al.[8]	A prospective cohort study	1–17 years	A nasopharyngeal aspirate or swab was analyzed by RT-PCR assay	The most prevalent pathogen was rhinovirus (29.4%). Among *non-rhinovirus pathogens*, RSV (8.8%), *influenza* (24.9%), and *parainfluenza* (34.1%) were associated with an increased absolute risk of treatment failure by 13.1%.
2	Saraya et al.[9]	Cross-sectional observational study	>18 years	Sputum or nasopharyngeal swabs were analyzed by RT-PCR.	Inpatients (75.3%) had a higher virus-positive rate than outpatients (19.3%). The most common VRIs were *rhinovirus* ($n = 24$), human *metapneumovirus* ($n = 9$), *influenza virus* ($n = 8$), and RSV ($n = 3$).
3	Seo et al.[10]	A prospective cohort study	>50 years	Sputum was analyzed by RT-PCR.	The RV virus was detected in both exacerbated and stable cases (32.4% vs 41.7%). IFV (20.6%), PIV (16.2%), and RSV (11.8%) dominated the exacerbated cases. In the stable cases, RSV (25.0%), PIV (16.7%), and IFV (16.7%) were noted.
4	Costa et al.[11]	A cross-sectional study	4–14 years	The nasopharyngeal swab specimens were analyzed by RT-PCR.	The most common virus was hRV (82.4), followed by FLUVA (15.0%), hADV (6.5%), hPIV2 (4.6%), hRSV (3.9%), FLUVB (2.6%) and hPIV1 (2.6%).
5	Alsuwaidi et al.[12]	A case-control study	3–6 years	Nasopharyngeal specimens were collected and utilized for RT-PCR.	The most commonly isolated organisms in both groups (patients and controls) were *Streptococcus pneumoniae, Haemophilus influenzae,* and *rhinovirus*
6	Amin et al.[13]	A prospective observational study	2–12 years	Nasopharyngeal or throat swabs that were analyzed by RT-PCR	A high prevalence of RSV (51.9%) and hMPV (24.9%) was observed among asthmatic patients with lower respiratory tract infections. 21.4% of patients who developed RSV infection required mechanical ventilation, 14.3% died, and 14.3% were admitted to the intensive care unit.

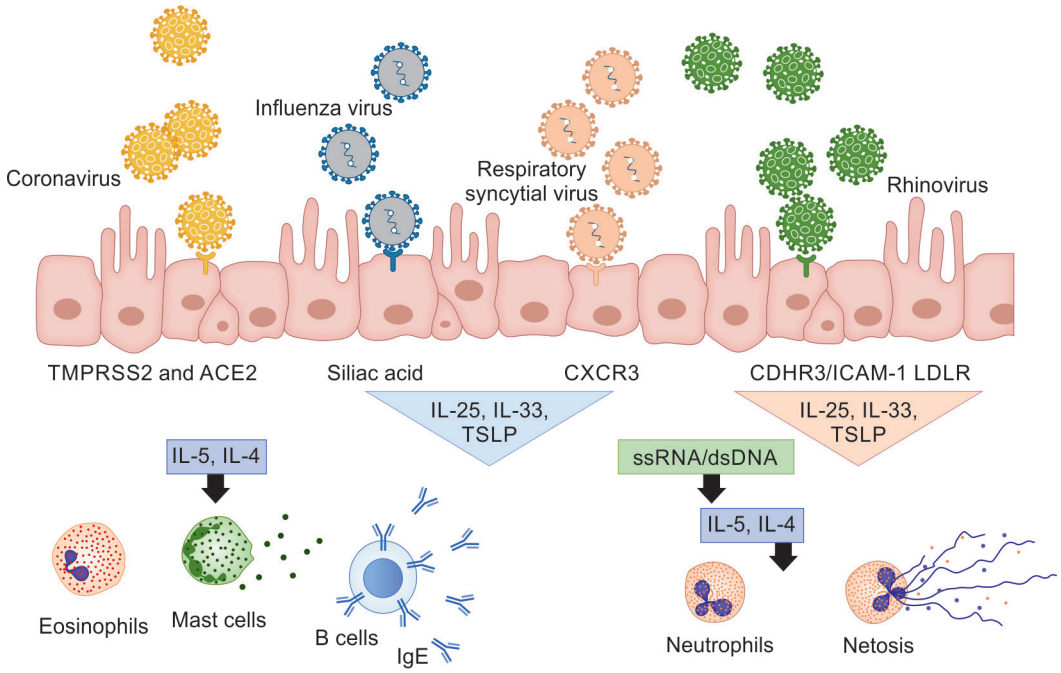

Fig. 2: Pathophysiology of viral-induced asthma

Moreover, Th1 cytokines cause neutrophils to activate. In an in vivo investigation, active neutrophils induced lung-specific conventional DCs to produce more high-affinity IgE receptors (FcRI). Hence, Th1 cells could increase type II inflammation.[34]

The release of chemokines including IL-8 and RANTES (CCL5), which attract neutrophils and mononuclear cells to the airway, is stimulated by viral replication in airway epithelial cells. Along with eosinophils already present in allergic airways, the recruited leukocytes contribute to the inflammatory environment by secreting more cytokines and mediators.[35]

Rhinovirus does not directly injure the epithelium; instead, it affects the host's reaction to allergens, irritants, and the environment through interacting with macrophages, T cells, and mast cells.[36–38]

Type I and type II immune responses are controlled by Th1 and Th2 T helper cells. Th1 cells secrete IL-2 and IFN-γ, which help type I immunity, which is characterized by phagocytic and antiviral activity, to develop.[39] Inflammatory cytokines including IL-4, IL-5, and IL-13, which are mostly secreted by Th2 cells, promote the Th2 type of immunity, which is characterized by eosinophilia and high antibody titers.[40]

Heightened Neutrophilic Inflammation of the Lower Airway

Airway secretions and, possibly, neighboring lung tissues contain substantial amounts of virus after viral replication in epithelial cells. It is believed at this time that large viral titers cause mononuclear cells to become activated and release many pro-inflammatory cytokines such as IL-1, IL-8, TNF, and IFN.

These cytokines are also strong inducers of the production of adhesion molecules, which in turn can activate other cells in the airway environment. This response serves as a powerful stimulation for the recruitment of inflammatory cells, primarily neutrophils, and T lymphocytes, together with chemokines produced by epithelial cells.

Patients with a higher neutrophil load are usually associated with exacerbation. Respiratory syncytial virus can cause severe wheezing and neutrophilic airway inflammation. Human rhinovirus generates nasal pro-inflammatory mediators, which are associated with neutrophilic inflammation.[41]

Direct Infection of the Lower Airway

The likelihood of exacerbations rises when the virus enters the lower respiratory tract directly. As it may lead to the destruction of the epithelial cells inflammation and airway obstruction. Several studies have connected RV with lower airway disorders such as bronchitis, bronchiolitis, and pneumonia.[42–44] Jartti et al.[45] report that high virus loads and multiple virus detections correlate to lower airway involvement. Lower airway sampling, typically bronchoalveolar lavage or induced sputum, is more sensitive and specific in diagnosing lower airway infections.

Genetic Association

More than 100 genes/loci have been linked to asthma by genome-wide association studies (GWAS). Asthma with severe exacerbations and wheezing episodes brought on by viruses are all connected with the first asthma locus found in GWAS, which is chromosome 17q21.[46,47] The sole known receptor for rhinovirus C is a transmembrane protein called CDHR3, which is abundantly expressed in airway epithelia (RV-C). Children who have a CDHR3 SNP (rs6967330) with a G to A base alteration have a higher risk of developing RV-C infections and experiencing severe asthmatic flare-ups. Early childhood asthma exacerbations, bronchiolitis, chronic rhinosinusitis, and early-onset adult asthma brought on by RV infections have all been linked to the CDHR3 asthma-risk genotype (rs6967330-A).[48]

Relation with Exacerbation

Exacerbations are deviations from the patient's regular state in terms of symptoms and lung function. Peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV1) measurements, when compared to the patient's prior lung function or projected values, can be used to quantify the reduction in expiratory airflow.[1]

Exacerbations typically result from several environmental factors, such as air pollution, smoke, cold or dry air, respiratory viruses, bacteria, allergies, and allergens. Up to 85% of asthma attacks in school-aged children and up to 50% in adults are brought on by viral infection.[31] Rhinovirus is the most common pathogen identified in adults and school-aged children with acute asthma exacerbations. Samuel and Busse stated that rhinovirus is associated with approximately 80% of acute wheezing episodes among school-aged children and 50% of acute wheezing episodes among adults.[49] Individuals with altered immune responses, namely those who have lower levels of cytokines such as type I interferon (IFN-α, IFN-β) and type III interferon (IFN-λ), are more likely to experience exacerbations.[48] It was found that IFN-λ had a crucial role in the etiology of asthmatic exacerbations and the clinical outcome of RV infection.[50] Considering that IFN-β is the factor that triggers this apoptosis in virus-infected epithelial cells, asthmatic patients exhibit much less of it than the general population.

Clinical Presentation

Asthma diagnosis is made on a clinical basis based on the history of the patient's symptoms. The presentation and severity of the illness vary widely. Over time, clinical characteristics can change between individuals and within the same patient. An important requirement in clinical evaluation includes the frequency with which symptoms develop, any aggravating or triggering circumstances, and the characteristics of a typical exacerbation.[3] Typical symptoms seen in patients with asthma are shortness of breath, cough, wheezing, and chest tightness. More than one of the symptoms may be present in the patient, they may worsen at night or in the morning, they may alter over time and in severity, and they may be brought on by a viral infection, an allergy, pollution, a change in the weather, smoke, or other irritants.[1] Some specific phenotypes have specific pathological features and clinical patterns depending upon the phenotype.[1]

Laboratory Diagnosis

Asthma is mostly diagnosed by reviewing the patient's medical history and evaluating lung function. Performing spirometry before and after bronchodilators will assist in validating the asthma diagnosis.

Pulmonary Function Tests

GINA recommends Measurement of lung functions in cases of exacerbations, if possible and without unduly delaying the treatment, PEF or FEV1 should be recorded before treatment is initiated.[1] Peak expiratory flow rate (PEFR) is the maximum flow rate generated during forceful exhalation. Forced expiratory volume (FEV) is the dynamic measurement of airflow using spirometry. In cases of acute exacerbations of asthma, regardless of the cause

of the exacerbation, there is a decline in pulmonary function.[51] Peak expiratory flow rate is measured using a portable flow gauge device. Peak expiratory flow rate measurements are the most used in-home monitoring of asthma. Peak expiratory flow rate is variable among individuals with similar body build. Eid et al. reported that for grading the severity of asthma, PEFR measurement might not be unreliable. Until the age of 5 years, spirometry cannot be reliably obtained in patients, and it is less useful in children than in adults.

(i) Blood Investigations: In cases of Eosinophilia and atopic disease, increased eosinophil counts can be seen in the peripheral blood smear. Eosinophils count >300 cells/μL in patients who are not on inhaled or oral corticosteroids. Normal counts of eosinophil can be seen in patients who are on corticosteroid therapy. Eosinophil counts are used to correlate the severity of the disease.[51] The presence of IgE-allergen-specific IgE can confirm an allergy to a specific allergen. IgE > 1,000 can prompt further investigations on the diagnostic possibility of allergic broncho pulmonary aspergillosis (ABPA). Need for anti-IgE therapy can be done based on IgE levels.

The severity of asthmatic acute exacerbations can be assessed using IgG levels. According to studies, low IgG levels are linked to viral infection-induced exacerbations and longer hospital stays. It was shown that patients with positive viral samples had lower blood IgG levels than patients with negative viral samples when researchers evaluated the serum IgG concentrations in patients suffering from severe virally induced asthma exacerbations.[52] Verduyn et al. Leitao et al.[53] studied the effect of serum IgG concentration in cases of COPD and found that patients with COPD having a low baseline IgG were associated with more exacerbations. Further research is needed to establish the precise role of IgG concentrations as a severity measure of severe asthma exacerbations.[51] Arterial blood gas (ABG) can be useful in cases of acute exacerbations who may present with hypoxemia.

(ii) Exhaled Nitric Oxide Level (FeNo): It is a non-invasive investigation to assess intrapulmonary eosinophilic inflammation. It is also used as a tool in the optimization of the management of asthma patients. Increased levels of alveolar No 2 are seen in cases of refractory asthma compared to the cases of mild asthma.[51] Malka J et al.[54] investigated the effects of viral infection on exhaled nitric oxide in children having asthma exacerbations and discovered higher FeNo levels in asthma patients who were reverse transcriptase polymerase chain reaction (RTPCR) negative, indicating eosinophil predominance in non-viral as opposed to viral exacerbations.

(iii) Chest Imaging: In mild to moderate cases of asthma, the radiological findings of the disease are relatively unremarkable. A severe asthmatic episode can result in hyperinflation of the lungs.[55] The presence of fleeting opacities can be seen in cases of ABPA. There is no specific role for chest imaging in the detection of viral-induced asthma.

(iv) Molecular Diagnostic Test (RTPCR): Exacerbations of asthma can be detected with molecular diagnostic tests such as RT-PCR, which detect viral etiologies. Contrary to conventional methods, it takes a short time to complete. There is a 100% virus detection rate using RTPCR in cases of viral-induced bronchiolitis, an 85–90% virus detection rate in children, and an 80% rate in adults experiencing asthma exacerbations.[7] In addition to detecting viral-induced asthma, RTPCR may detect its exacerbations.

Management

The key to effective management is a multifaceted approach that combines pharmacological interventions, and preventive measures and emphasizes the importance of personalized treatment plans tailored to the severity of the disease and improving overall quality of life.

Bronchodilators

Bronchodilators are the mainstay management in the treatment in cases of acute exacerbations, β2 agonist activates the β2 receptor and causes bronchodilation. During acute exacerbations of asthma/severe asthma, Nebulized form, or inhaled forms of short acting beta agonist (SABA) (salbutamol or levosalbutamol) can be used every 15–20 minutes in the first 1 hour if the exacerbation doesn't come under control. Short acting beta agonist is used for symptomatic relief in patients with asthma, it has no role in reducing inflammation. According to GINA guidelines, SABA is not a preferred form of reliever but can be used as an alternative to low-dose maintenance inhaled corticosteroid (ICS) in asthma management.[1] Short acting beta agonist can be used in cases of acute exacerbations induced by viruses to improve the symptoms and lung function.

Corticosteroids

Depending on the severity and exacerbation state of asthma, steroids are utilized in three different ways. As per GINA recommendations, low-dose ICS-Formoterol is the preferred reliever.[1] For one week, oral prednisolone 40–50 mg can be used to minimize exacerbations in some individuals, even those who have symptoms, and an adequate exacerbation.[1] Intravenous administration may be necessary for patients with severe asthma who need to be hospitalized.[1] They play a part in maintaining disease management and averting future exacerbations in situations where there is an acute exacerbation.

The role of ICS in preventing virus-induced asthma exacerbation other than anti-inflammatory properties is poorly understood. Inhaled corticosteroid forms a major part of the management of asthma. Low-dose ICS + long-acting beta agonist (LABA) (Formoterol) preferred controller and reliever in the initial treatment of asthma with fewer symptoms and step-down treatment for patients with asthma exacerbations.[1] The synergistic effect of both ICS and LABA on airway inflammation accounts for the decline in exacerbations. Long-acting beta agonist has been shown to boost ICS's anti-inflammatory and anti-proliferative effects, as well as to reduce chemokine production by *rhinovirus (RV)*-infected BEC that could be immune pathogenic (BECs).[56] Despite optimal use of corticosteroid, viral induced asthma occurs.

Leukotriene Antagonists

The drug has not been proven to reduce exacerbations in any significant way. In a study by Weiss et al.,[57] montelukast was shown to not be as effective as a placebo in easing the burden of asthma in children. An evaluation of the effects of montelukast in acute and chronic post-viral wheezing by Kanchanateeraphong et al.[58] shows that the drug improves patient outcomes.

Muscarinic Antagonists

These agents are usually preferred as an add-on in the management of asthma. Based on a systematic evaluation of 13 randomized placebo-controlled trials, tiotropium decreased the frequency

of exacerbations and improved asthma control in patients with moderate symptomatic asthma who were previously using medium-to-high doses of ICS or ICS/LABA.[59,60] A short-acting muscarinic antagonist (ipratropium bromide) may be beneficial to asthmatic patients under regular treatment as well as those experiencing severe asthma exacerbations because they improve respiration more rapidly and significantly.[61] Muscarinic antagonists, which are frequently used in the therapy of asthma and exacerbations, are ineffective against asthma and exacerbations brought on by viruses.

Macrolide Antibiotics

Macrolide along with its bactericidal action, has anti-inflammatory and anti-viral activity. Out of the macrolide, azithromycin decreases rhinovirus replication by activating IFN and interferon-stimulated genes (ISGs).[62] Azithromycin's effects on asthma exacerbations and quality of life in patients with chronic uncontrolled asthma were researched by Gibson et al.[63] The 48-week trial revealed that taking azithromycin three times a week reduced asthma attacks and improved quality of life. It was found that azithromycin caused no clinically significant benefits in cases of acute asthma exacerbations according to Johnston et al.[64] A prospective study is needed to investigate macrolides other than azithromycin and their role in the combating of viruses.

Targeted Biological Therapy

(i) Omalizumab: Omalizumab is a humanized monoclonal antibody targeted against immunoglobulin E (Ig E). The use of Omalizumab is advised in patients aged more than 6 years with associated poorly controlled moderate to severe asthma.[1] Exacerbations are decreased, and antiviral defense mechanisms are strengthened by raising the level of IFN release in response to *rhinovirus* stimulation from peripheral blood mononuclear cells.[65]

(ii) Type I IFN Therapy: Interferon therapy in cases of acute exacerbations of asthma is still poorly understood. Inhaled INF-β showed rates of acute exacerbations and resulted in increased lung functions. IFN-β also has Th2 antagonistic actions, this acts in two ways; Firstly by reducing the inflammation driven by the virus and slowing down the Th2 response to allergens.[66]

(iii) Toll-like Receptor 7/8 Agonists: Toll-like receptor 7/8 is expressed by dendritic cells, macrophages, and perhaps other myeloid or lymphoid cells. Toll-like receptor 7/8 agonists are effective in treating allergy conditions including asthma. Current research on TLR 7 agonists has revealed protective effects that lessen pulmonary function impairment and eosinophilic inflammation.[67] Toll-like receptor 7 agonist in nasal formulation for cases of allergic asthma is under phase 2 trial (NCT02833974).

(iv) Virus-specific Antibody: Monoclonal antibodies contained in palivizumab bind to the RSV surface protein F and exert high activity against group A and B viruses. Since 1999, palivizumab (Synagis) has been available in several countries after being licensed in June 1998 in the United States.[68] The second-generation monoclonal antibody developed after Palivizumab is motavizumab.[69] In a 6-year follow-up study, H. Mochizuki et al.[70] investigated the impact of palivizumab on the prophylaxis of preterm infants and the development of subsequent wheezing. They discovered that while it did not affect the children's development of atopic asthma, it did have an impact on the frequency of subsequent wheezing episodes.

Vaccination

Annual influenza vaccinations are effective at preventing infection and reducing morbidity.[71] E Vasileiou et al.[72] conducted a systematic review and meta-analysis of influenza vaccination in asthma patients. Research shows that getting vaccinated against the flu reduces asthma-related emergency room visits by 59–78%. In addition, patients who received vaccination did not experience an increase in asthma flare-ups. Mejias et al. stated that there are no licensed vaccines for RSV despite the burden associated with the disease and 60 years of active research. RSV vaccine development has been hindered by safety concerns after the first vaccine was developed in the 1960s.[73]

The SARS-Cov-2 (COVID-19) infection had no significant effects on people with well-controlled asthma. However, those with asthma who required oral corticosteroids had a higher risk of infection.[74] At present there is no contraindication for vaccination against COVID-19 in patients with asthma, unless the patient has an allergy to any product of the vaccine.[1]

Personal Preventive Measure

Hand washing and the wearing of respiratory masks are simple precautions that have been proven to be successful in reducing the transmission of viral agents due to the considerable potential of viral propagation through droplets and fomites. There is no specific treatment available for most respiratory viruses, except a few. Precautionary measures like proper hand washing and wearing masks in public places can reduce the risk of acquiring infection.

Impact of the COVID-19 Pandemic on Asthma

The World Health Organization (WHO) named COVID-19, the coronavirus pandemic brought on by SARS-CoV-2, a global hazard in December 2019. By January 2023, 66,84,756 people had already died because of COVID-19 worldwide. As previously mentioned, early respiratory viruses are the cause of acute exacerbations in asthma sufferers. The association between asthma and SARS-Cov-2, its involvement in the severity of the disease in asthma patients, roles in exacerbations and outcomes, etc., were all investigated during this COVID-19 pandemic induced by SARS-Cov-2.

Respiratory illness is one of the most common factors for exacerbations of asthma. During the pandemic, it was expected that there would be an increased morbidity in people with asthma who contract COVID-19 infection. However, the number of asthmatics contracting the virus and having a greater risk of mortality was also found to be low.

Richardson et al.[75] US-based study in New York City on a total of 5700 COVID patients, in which 479 (9%) patients were identified with asthma. De Boer et al.[76] found that the exacerbations associated with asthma were reduced during the pandemic. The reason was stated to that being to social distancing which was followed strictly during the pandemic. However, the downfall of the study was the population size was relatively small.

Tydeman et al.[77] a UK-based study on rebound exacerbations following the lifting of restrictions over COVID-19. The study concluded that after the lifting of restrictions, there was an increase in acute respiratory illness and asthma exacerbations which was due to social gatherings and less use of face masks.

In Japan, Matsumoto et al.[78] investigated how the COVID-19 pandemic affected the onset of childhood asthma brought on by respiratory viral infections. They discovered that after the start of

the COVID-19 pandemic, both the diagnosis of new childhood-onset asthma and the incidence of Rhinovirus and RSV infections in children decreased.

The pandemic led to an upsurge in telemedicine consultations for the safe and practical management of patients remotely. The limitations were the inability to do objective measurements including spirometry, PEF, pulse oximetry, FeNo2, and auscultation.[79]

Taquechel et al.[80] investigated the impact of the COVID-19 pandemic on changes in air pollution, viral testing, and the use of healthcare services for children with asthma. There were no appreciable improvements in air pollution, but after the pandemic, telemedicine consultations became more popular and the incidence of respiratory virus infections among children decreased. Because the study's data came from a single institution, we are unable to extrapolate its conclusions from it.

Because of the COVID-19 infection control recommendations, spirometry has been employed less frequently to stop the spread of infection. Using an inline filter during spirometry helps reduce the spread of infection, but coughing during the test puts you in danger.[1]

According to the GINA report, a vaccine against COVID-19 is safe for asthma patients. Patients with allergies to specific vaccine ingredients can choose another COVID-19 vaccine. Vaccine administration should be delayed in patients with fever or infection.[1]

Impact of Asthma on COVID-19 Outcomes

The entry of SARS-CoV-2 into the host is mainly through the ACE-2 receptors of the host. Increased expression of ACE 2 receptors and its association with high infectivity of SARS-CoV-2 infection has been established in some studies.[81]

Th2 endotypes in asthma patients have a protective effect because they improve viral clearance from the airway, lower ACE2 expression, and lower pro-inflammatory cytokine production. According to Jee Myung Yang et al.,[82] who researched allergic disorders and susceptibility to the severity of COVID-19, individuals with nonallergic asthma had a greater rate of SARS-CoV-2 test positivity and worse clinical findings for COVID-19 than those with allergic asthma.

Experimental studies suggest that eosinophils may aid in the clearance of respiratory viruses and the antiviral host defense, which raises the hypothesis that asthma patients with type II inflammation, marked by an elevated eosinophil count in the airways, may be protected against severe COVID-19 effects.[83]

Sunjaya et al.[84] compared the risks of COVID infection in the group of people with asthma to those in the group of people without asthma, they came to the conclusion that the risk of COVID infection was lower in the asthma group.

In a study by Ren et al.[85] on the impact of allergic rhinitis and asthma on COVID-19, it was discovered that, in those under the age of 65, both disea0073xzes were protective against COVID-19 infectivity. One aspect of the protective effect, as previously mentioned, was decreased expression of ACE 2 receptors in the airways of those with allergic inflammation.

The allergic asthma patients were found to have lower ACE 2 expression compared to that of non-allergic asthma patients.[86] The allergic asthma patients having Th 2 response leads to activation of IL-4, IL-13 which is associated with reduced expression of ACE 2 in the epithelial cells present in the airway.[21]

According to Peters et al.[87] using ICS significantly reduced ACE2 and TMPRSS2 receptor expression, resulting in a lower incidence of COVID-19 in asthma patients. However, the study was inconclusive and recommended additional prospective studies.

Asthmatic patients with well-controlled asthma have better outcomes than those who have poorly controlled asthma, often needing oral corticosteroids or hospital admission, resulting in severe outcomes.[1] Shi et al.[88] National cohort study on COVID-19 outcomes in adult patients with asthma, the study concluded that asthma patients who required the need for use of oral corticosteroids courses or needed hospital admission were associated with increased COVID-19 hospitalization and as well as death.

Summary

Viral infections are important triggers of the inception and exacerbation of asthma. Several studies have demonstrated that RSV and rhinoviruses cause significant airway inflammation that causes asthma and its exacerbations, most likely due to impaired type I immunity. There are no specific drugs approved for use on the market, and trials are still ongoing for drugs that fight certain viruses. The use of targeted biological therapy and vaccinations may, however, be more effective in preventing infection and reducing morbidity. Thus, taking prophylactic steps lowers the risk of developing viral infections, their associated morbidity, and their danger.

As a result of our findings, we suggest that by adopting prevention and management strategies that are region- and population-specific, such as vaccines and rapid diagnostics, health authorities could reduce the burden of disease.

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