International Immunopharmacology 91 (2021) 107309

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

A review on the effect of COVID-19 in type 2 asthma and its management

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Type-2 asthma
Cytokines
Inflammation
T-cells

ABSTRACT

Background: COVID-19 is considered the most critical health pandemic of 21st century. Due to extremely high transmission rate, people are more susceptible to viral infection. COVID-19 patients having chronic type-2 asthma prevails a major risk as it may aggravate the disease and morbidities.
Objective: The present review mainly focuses on correlating the influence of COVID-19 in type-2 asthmatic patients. Besides, it delineates the treatment measures and drugs that can be used to manage mild, moderate, and severe symptoms of COVID-19 in asthmatic patients, thus preventing any exacerbation.
Methods: An in-depth research was carried out from different peer-reviewed articles till September 2020 from several renowned databases like PubMed, Frontier, MEDLINE, and related websites like WHO, CDC, MOHFW, and the information was analysed and written in a simplified manner.
Results: The progressive results were quite conflicting as severe cases of COVID-19 shows an increase in the level of several cytokines that can augment inflammation to the bronchial tracts, worsening the asthma attacks. Contradicting to this, certain findings reveal the decrease in the severity of COVID-19 due to the elevation of T-cells in type-2 asthmatic patients, as prominent reduction of T-cell is seen in most of the COVID-19 positive patients. This helps to counteract the balance of immune responses and hence ameliorate the disease progression.
Conclusion: Asthmatic patients must remain cautious during the COVID-19 pandemic by maintaining all the precautions to stay safe due to limited research data. Future strategies should include a better understanding of asthmatic exacerbation and its relation to COVID-19.

1. Introduction

Coronavirus represents the group of viruses that are relatively ubiquitous in the environment, affecting human, bird, and animal that is predominantly responsible for common cold and fever [1]. It is believed that SARS-CoV-2 has originated from bats and jumped to pounce the human species via some sort of adaptation [2]. It first emerged from a seafood market in Wuhan, China. The traces of SARS-CoV-2 were found in bats who were reckoned as its natural reservoir. Later, other animals like civet cats, pangolin, and raccoon dogs were also comprehended to

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; COVID-19, Coronavirus Disease-19; NIH, National Institutes of Health; NSAIDs, Nonsteroidal Anti-Inflammatory Drug; ACE inhibitors, Angiotensin-Converting Enzyme Inhibitors; AHR, Airway Hyper-Responsiveness; TSLP, Thymic stromal lymphopoietin; NK Cells, Natural Killer cells; FVC, Forced Vital Capacity; PEF, Peak Expiratory Flow Rate; FEV1, Forced Expiratory Volume In The First Second; FeNO, Fractional Exhaled Nitric Oxide; STAT-6, Signal Transducer And Activator Of Transcription-6; JAK-2/STAT-5, Janus Kinase-2/Signal Transducer And Activator Of Transcription-5; M-CSF, Macrophage Colony-Stimulating Factor; POSTN, Periostin Gene; ORF, Open Reading Frames; RBD, Receptor-Binding Domain; TMPRSS2, Transmembrane Protease, Serine 2; Rdrp, RNA-Dependent RNA Polymerase; HLA, Human Leukocyte Antigen; CDC, Centres For Disease Control And Prevention; HRV, Human Rhinovirus; AERD, Aspirin-Exacerbated Respiratory Disease; FRC, Functional Residual Capacity; ERV, Expiratory Reserve Volume; TNF-α, Tumor Necrosis Factor-Alpha; ACOS, Asthma-COPD Overlap Syndrome; COPD, Chronic Obstructive Pulmonary Disease; GINA, Global Initiative For Asthma; FRU, First Referral Units; HFNC, High Flow Nasal Cannula; DPPC, Dipalmitoyl Phosphatidyl Choline; NRDS, Neonatal Respiratory Distress Syndrome; SP, Surfactant Protein; HRCT, High-Resolution Computed Tomography.

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https://doi.org/10.1016/j.intimp.2020.107309
Received 15 October 2020; Received in revised form 6 December 2020; Accepted 7 December 2020
Available online 30 December 2020
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be intermediate hosts. COVID-19 outbreak was proclaimed as a Public Health Emergency of International Concern on 30th January 2020 by the World Health Organisation (WHO), and as a global pandemic on 11th March 2020 [3]. The key reason behind its widespread is on account of its high reproduction number (R_0) which was found to be ranging from 1.4 to 3.8, signifying that on average, one infected person is transmitting the infection to 2.6 healthy persons. The pandemic will amplify until the R_0 becomes less than 1 [4,5]. Recently, on 7th October 2020, total active cases of COVID-19 reached near to 36,283,370 with USA, India, and Brazil being mostly affected countries. More than 27,304,644 have been recovered, but around 1,057,957 have lost their lives. In India, around 6,832,646 people were confirmed with active cases of COVID-19 with a recovery of 5,821,423 (around 85%). It has an average incubation period of 5.1 days (2–14 days). Major symptoms of COVID-19 are fever, fatigue, dry cough, muscle pain, dyspnoea, pneumonia, and in many cases reduced leukocyte counts. Less common symptoms include sore throat, diarrhoea, conjunctivitis, headache, rashes on the skin, or discolouration of fingers or toes [5].

Asthma is a non-communicable, chronic respiratory disorder in the lower airway tract that affects people of all ages. It is characterised by rising responsiveness to the tracheobronchial tree by the influence of numerous external stimuli that ultimately leads to narrowing of the airway tract and many other consequences. According to 1991, 1997 and 2007 NIH guidelines (National Institute of Health), asthma is defined as "a chronic inflammatory disorder that affects the airways in the lungs and involves many cells and cellular elements" [6,7]. It has become a common disorder with around 339 million people suffering from some kind of asthma worldwide. Maximum number of deaths due to asthma aggravation is seen in developing countries. In India, it is found that every 3 people are asthmatic out of 100 adults. The most common symptoms of asthma include paroxysms of cough, wheezing, shortness in breathing (dyspnoea), and tightness in the chest [6,8]. There are numerous allergens that can trigger bronchus to cause bronchoconstriction, infection in the respiratory tract, initiate allergic responses, and narrowing of the airway tract, causing obstruction in breathing. Not only allergens are responsible for these responses, but also it can be initiated by exercise and some drugs such as NSAIDs (ibuprofen and naproxen); β-blockers; morphine; Angiotensin-converting enzyme (ACE) inhibitors including lisinopril and enalapril (by developing cough) as well [9]. It's a systemic disease that initiates the activation of many inflammatory cells, thus leading to permanent changes in the bronchi; and these changes in the structure of the airways are known as airway remodelling. These changes occur due to multiple inflammations along with the matrix protein and growth factor produced by the inflammatory cells. Episodes of damage and repair of epithelium cause modification of the cells in the airway. Such modifications cause loss of the contraction and dilation ability due to its elasticity impairment, accumulation of fluid in the cells or oedema and increase in the number and size than a healthy person [10].

The pathogenesis involves many phenotypical changes, which are visible characteristics and endotypes underlying the molecular mechanism. Asthma activates the immune system, airway hyperresponsiveness (AHR), activation of epithelial cells, overproduction of mucus, and ultimately causes permanent airway obstruction [11]. The immunological mechanism of asthma involves both adaptive and innate immunity that includes eosinophils, type-2 innate lymphoid cells, T helper type-2 (TH2) cells, and IgE-secreting B cells. The narrowing of the airways results from the chronic inflammation in the airways and invasion of inflammatory cells such as eosinophils, neutrophils, lymphocytes, macrophages, and mast cells. Airway hyperresponsiveness (AHR) is one of the important physiological characteristics of asthma [12]. The excess mucus production by the B-cells causes obstruction in the airway passage. Airway remodelling which involves enlargement of the goblet cells, excess deposition of collagen in the subepithelial region, reduction in quality of epithelial and cartilage, enlargement of smooth muscle cell of the airways and thickening of the airways. These changes are reversible put due to repeated episodes of remodelling, which can result in permanent damage to the airways [13,14].

2. Type-2 inflammation in asthma

Inflammation occurs in the airway due to systemic allergic response that may lead to aggravation of asthma and lowers the functioning of the lungs [15]. Cytokines are majorly held responsible for these inflammations. Type-2 immune responses are established with the stimulation of cytokines such as IL-4, IL-13, IL-17E (IL-25), IL-33, and thymic stromal lymphopoietin (TSLP) [16]. Upon the entry of allergens, pollutants, and different kinds of viral infections, all the mechanisms occur only once. The cells that are responsible for triggering the allergic response are TH2 cells (helper T cells; also known as CD4+ cells), IL-C2 cells, IgE-producing B-cells, NK cells, eosinophils, basophils, and mast cell [17,18].

The important components to be diagnosed to confirm type-2 asthma are: 1) To get proper evidence of obstruction in the airways with the help of spirometry, which tests the pulmonary functions like forced vital capacity (FVC), peak expiratory flow rate (PEF), the total volume of air forcefully exhaled from the lungs in one breath and forced expiratory volume in the first second (FEV1) [19,20]. In children, a decrease in FEV1/FVC ratio less than 0.9 or below the lowest 5% of the reference population confirms respiratory obstruction. In adults, obstruction is confirmed if the FEV1/FVC ratio is less than 0.80 (according to GINA guidelines) or below the lower limit of normal (lowest 5% of the reference population) [21]. 2) After the confirmation of the airway obstruction with the aid of spirometry, the next step is to check whether the asthma is atopic or non-atopic. Allergy examination is usually performed by quantifying the presence of IgE in the serum or by skin testing method. Fractional exhaled nitric oxide (FeNO) testing can be done on an optional basis to diagnose asthma in both adults and children [19,21].

Asthma is generally considered a TH2 disease. Studies have proven that IL-4 has pathophysiological effects concerning asthma. With the binding of IL-4 to the IL-4Rα receptor, it forms a heterodimer along with a couple of receptors on the surface: IL-2γc or IL-13Rα1, followed by phosphorylation of signal transducer and activator of transcription-6 (STAT-6) and GATA3 [22]. All this innate response contributes highly to airway inflammation which is associated with eosinophils, basophils, IL-C2 cells, and mast cells. Based on the level of TH2 produced, the pathophysiology of asthma can be classified into TH2 elevated or TH2 inferior phenotypes [23]. TH2 cells secrete IL-4, IL-5, and IL-13, which amplifies the formation of B-cell to produce IgE and also eosinophils. Mucus generation, airway obstruction, muscle hypertrophy, and hyperactivity reactions are the derived outcomes of the inflammation. IL-4 is expressed as an upstream cytokine that exercises its function over the allergic response by advocating TH2 cell differentiation and formation of IgE. IL-4 highlights a wide spectrum of biological activities and could be considered as the major cytokine taking part in the pathogenesis of allergic disorders. Stimulation of mucus-producing cells and fibroblast is an important result of asthma, indicating the role of IL-4 in the pathogenesis of airway remodelling. Expression of vascular cell adhesion molecule-1 on endothelial cells is another important activity of IL-4 in inflammation caused by allergic reactions. This leads to an increased adhesiveness of endothelium for monocytes, T-cells, basophils, eosinophils, which are the defining features of an allergic reaction [24,25].

The stimulated helper-T cell population is the leading source of Interleukin-5, however, secretion from other source have also been observed, which includes mast cells, eosinophils, CD4+ and CD8+ T-cells. It gets activated by its specific binding to the α-chain of the receptor and once chain shared with IL-3 through the pathway of JAK-2/STAT-5 to release M-CSF [26]. IL-5 increases the number of eosinophils in sputum causing hyperresponsiveness in asthmatic patients. This cytokine is highly definite for eosinophilic inflammation and antibodies that block the IL-5 activity, widely effective in decreasing inflammation

and airway hyperresponsiveness. Deep-rooted clinical studies are in progress and should resolve the therapeutic aid of IL-5 antagonism in asthma [27,28].

IL-9, released from different cells like mast cells, TH2 cells, and ILC-2 cells, initiates the amplification of triggered T-cells and differentiation of mast cells. It also stimulates the secretion of IgE from B-cells and mainly mast cells to respond to the allergens by elevated cell surface expression of FcεRI receptors. IL-9 also impedes the over secretion of mucus and expands regulation of epithelial cell genes by IL-13 [29,30].

IL-13 originates from triggered T-lymphocytes, B-lymphocytes, and mast cells. IL-13 is a cytokine that is in association with IL-4 and binds to IL-4 alpha receptor, which is also expressed in asthmatic patients by TH2 cells [31]. Reports related to increased expression of IL-13 mRNA have been found in the airway mucosa of patients with both atopic and non-atopic asthma. The changes in the airway that occurs as a result of allergy were found to have IL-4 playing a vital role for the initial TH2 formation during early sensitisation but IL-13 release is of more value during secondary antigen unfolding [31,32].

In response to the epithelial regulation of type-2 allergic response, TSLP, IL-25, and IL-33 play a crucial role as mediators of type-2 inflammation. These cytokines alarm the immune system to any external stimuli and regulate tissue re-imposition after injury. These cytokines govern type-2 immunity and are also known as "alarmins" released by barrier epithelium. They also play major roles in initiating inflammation during allergic disease aggravation and may act as a key target for the therapeutic establishment once the disease is well occupied [33–35].

Genetic factors also play its part in asthma associated with type-2 inflammation. It is observed that either both or one of the parents have type-2 inflammation asthma, then the offsprings are four times more liable to get affected by any allergic disease or asthma. Biomarkers have found a potential use in asthma treatment as they assist in the process of understanding the disease severity, its breakthrough, and the pathology of any underlying disease. In the era of precision medicine, biomarkers need to play a crucial role in finding out susceptibility, the response of a disease to a particular and specific treatment. IgE, eosinophil count, the fraction of exhaled nitric acid, and periostin (POSTN, or osteoblast-specific factor; OSF-2) has turned up to be some habitual asthma biomarkers. The potential use of biomarkers in asthma includes its diagnosis, finding out the severity of the disease, defining disease endotype, possible treatment measures, treatment response, reduce the risk of disease exacerbation and inhibit the declining function of the lung [36–38].

3. An overview of the virus: SARS-CoV-2

Coronavirus disease 2019 (COVID-19) is a zoonotic disease transmitted to humans, especially from animals and is caused by a β group of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreading widely among humans all over the globe [39]. It is the third highly pathogenic form of coronavirus leading to pandemic after the Middle East Respiratory Syndrome coronavirus (MERS-CoV) and the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) [40]. SARS-CoV-2 is an enveloped nonsegmented, positive-sense single-stranded RNA virus (Baltimore class IV) belonging to the *Coronaviridae* family of order- *Nidovirales*. It has a diameter of about 60–140 nm with a size of 27–32 kilobases [41,42]. It is milder than the other coronavirus that had caused a pandemic, but the main drawback is its high community spreading rate. Epidemiological studies have shown its spherical or pleomorphic shape with about 14 open reading frames (ORFs). ORF1a and ORF1b are the first ORF encoding replicase proteins, while the other ORFs encode for the structural proteins including nucleocapsid (N), envelope (E), spike (S), and transmembrane glycoprotein (M) [43,44]. Spike protein contains peplomers that jut out from the virion surface making it appear like a crown under the cryogenic electron microscope, from where the virus is named. Mutation in the spike protein is responsible for the zoonotic transmission of SARS-CoV-2 [45]. The main mode of transmission is through respiratory droplets, secretions, and saliva shed by an infected person who is in close contact (within 1 m) with another person and invades via T-zone of the face (eyes, nose, and mouth). Till now, no cases of faeco-oral transmission of the COVID-19 virus has been reported. On 9th July 2020, the WHO acknowledged some reports of airborne spread of the SARS-CoV-2 virus. After entering the host cells, it rapidly divides in the ciliated epithelium of the respiratory tract [46].

The virus enters the host cell by two mechanisms: one via plasma membrane fusion or the other via endosome formation (Fig. 1). A particular region of the spike protein of the virus called receptor-binding domain (RBD) which is present at the C-terminus of S1 subunit, interacts with the angiotensin-converting enzyme 2 (ACE2) receptors of the host [47]. The transmembrane protease, serine 2 (TMPRSS2) breaks the spike protein activating the fusion proteins located at the S2 subunit that fuses with ACE2 receptors [48]. By another mechanism, an endosome is formed around the virion that enters the cell by the action of pH-dependent cysteine protease, cathepsin-L and releases RNA into the host cell, thus infecting them. The activated ORF1a and ORF1b are then translated into pp1a and pp1ab polyproteins, respectively [44]. These proteins are then cleaved by papain-like proteases (PLpro) and chymotrypsin-like protease (3CLpro or Mpro) into about 16 non-structural proteins (nsp 1-16) [49]. Furthermore, certain nsps form a replicase-transcriptase complex (RTC) or RNA-dependent RNA polymerase (RdRp), which then develops into several subgenomic mRNAs by transcription and finally leads to the formation of subsequent viral proteins (N, E, S, M, and many more) by translation at the endoplasmic reticulum bound ribosome [50]. These formed proteins and RNA genomes are further assembled at the endoplasmic reticulum and Golgi apparatus and form new virions inside the vesicles that are later released out from the cells to complete its life cycle.

Till now, no registered vaccine has been marketed for proper immunisation against SARS-CoV2, but many are under clinical trials, hoping for their successful trial. In that case, our body's immune system plays a major role in defence against the virus. Both cell-mediated and humoral immune response is observed. After the entry of the virus, it is being targeted by antigen-presenting cells (APC) like macrophages, which engulfs (phagocytose) them and entraps into phagosomes [51]. Lysozymes are released into it, causing the lysis of the virus, leaving only the antigenic portions. Chromosome 6 of the APC undergoes several transcriptions and translations to form appropriate human leukocyte antigen (HLA) complex, specifically major histocompatibility complex-2 (MHC-2) proteins are formed, which brings those antigenic proteins to the surface and travels throughout the lymphatic system in the search for appropriate T helper cell (CD4+). Activation of helper T cell occurs when the antigen binds to the T-cell receptor (TCR) and the MHC-2 binds with CD4 domain [52]. After then, a series of mechanisms runs causing the release of various cytokines like IL2, IL4, IL5, IL17, and other proinflammatory cytokines through NF-kB signalling pathways, which ultimately amplifies the production of antigen-specific antibodies by the activation of B-cells (Fig. 2) [53]. Moreover, the cytotoxic T cells (CD8+) directly kill those viruses by activating granzymes and perforins. It has been observed that the person with SARS-CoV2 infection develops IgG and IgM antibodies after 6–15 days of infection. According to a study conducted by Zhao J. et al., less than 40% of the antibodies are produced within the first week of infection, but after 15 days of onset, the levels suddenly increases to 100.0% of total antibodies, 94.3% increase in IgM and 79.8% elevation of IgG [54]. To break the spread of the virus among people, the government of India launched a national lockdown from March 25, 2020. Currently in India, COVID-19 is diagnosed by Real-time PCR test (RT-PCR) as a confirmatory test with a rapid antibody test as a supplementary tool [55].

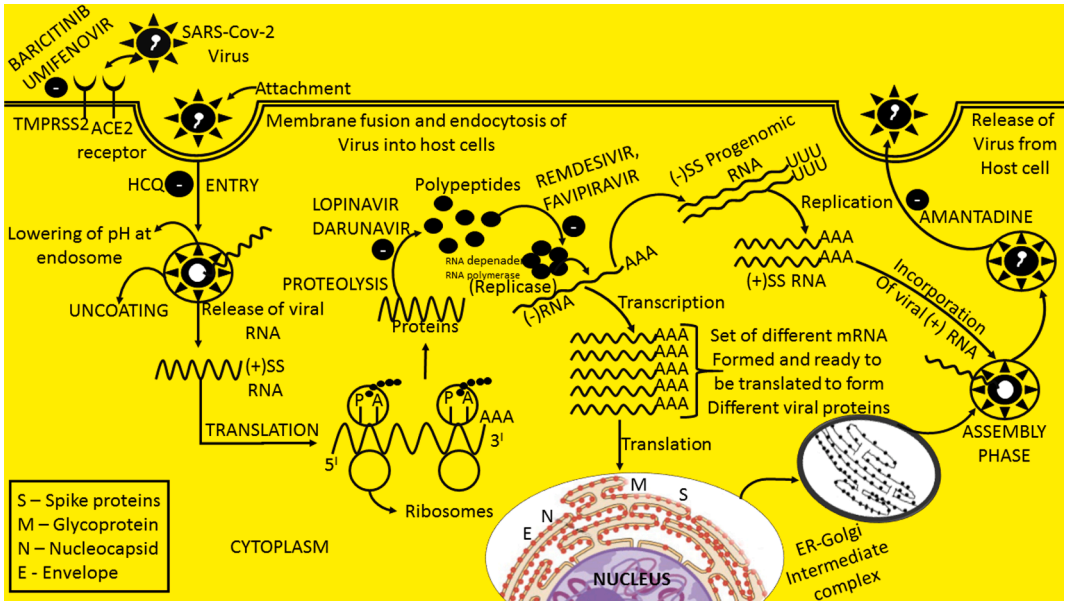

Fig. 1. The life cycle of SARS-CoV-2 virus. The virus gets its entry into the host cells by either plasma membrane fusion or other via endosome formation. The receptor-binding domain (RBD) at the C-terminus of S1 subunit of the spike protein (S) interacts with the angiotensin-converting enzyme 2 (ACE2) receptors of the host and binds to it. On the other hand, TMPRSS2 breaks the spike protein activating the fusion proteins located at the S2 subunit which fuses with ACE2 receptors and enters the host cell. The virions are taken up by the endosomes and by acidification of the endosome, RNA is released into the host cell. The activated part of genomic RNA, ORF1a and ORF1b are then translated into pp1a and pp1ab polyproteins, respectively which are later cleaved into 16 different non-structural proteins (nsp 1-16). Many of these nsp form replicase which initiates the formation of subgenomic mRNAs by transcription and forms viral proteins like N, E, S, M. These proteins are further assembled at the endoplasmic reticulum (ER) and later at Golgi apparatus to form new virions inside the vesicles that are released out from the host cells to complete its life cycle.

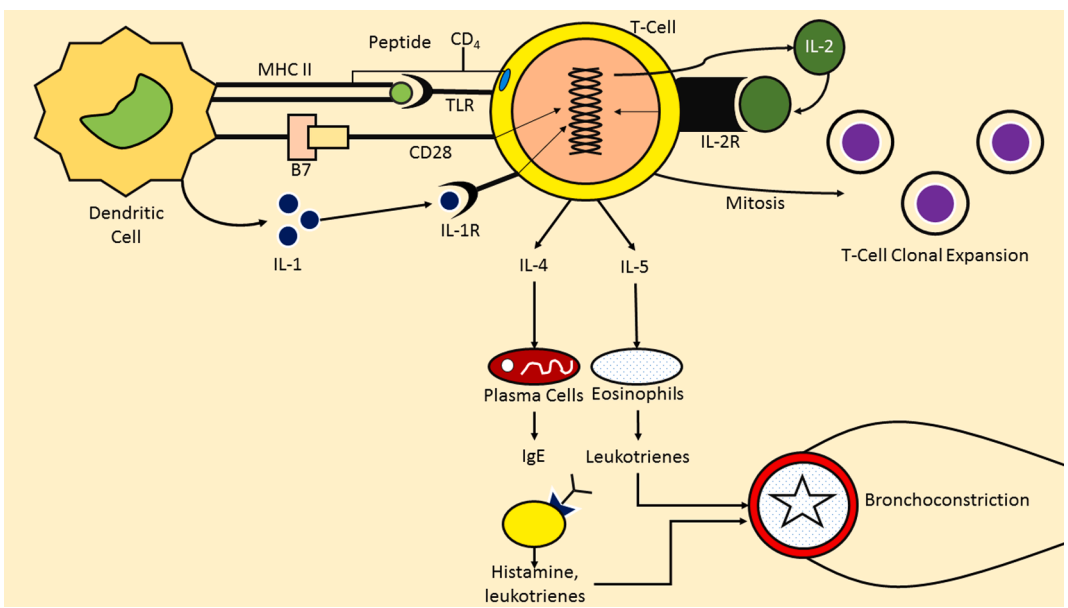

Fig. 2. Schematic diagram depicting the activation of T-cells and B-cells in response to specific allergens. After phagocytosing the allergen by the antigen-presenting cells (APC) such as dendritic cells or macrophages, it only presents the antigenic portion of the allergen and synthesises specific MHC II proteins against the antigen. The MHC II protein brings the antigen to its outer surface and the APC moves throughout the lymphatic system and searches for appropriate T-cells. After finding suitable T-cells, the antigenic portion binds to T-cell receptor (TCR), MHC II binds with CD4 with some additional interactions between B7 and CD28 of APC and T-cell respectively. This activates IL-2 which binds with the autoreceptor IL-2R located at T-cell and undergoes mitosis to form more T-cells. T-cells then release IL-4 which activates B-cells that form IgE antibodies. IL-5 activates eosinophils that release leukotrienes and histamines. All these mediators cause potent broncho-constriction leading to allergic asthma attacks.

4. Epidemiology and different factors influencing type-2 asthma

Asthma is quite a common but non-reportable disease due to which many asthmatic patients remain undiagnosed. According to an epidemiological study conducted in Russia, only 6.9% of the adults were previously diagnosed with asthma, whereas 25.7% of that same population reported asthma symptoms like wheezing or breathlessness that were not diagnosed earlier in their life [56].

4.1. Worldwide implications

According to The World Health Organisation, in 2016, there were approximately 339 million people (4.5% of the world's total population) globally suffered from asthma [57]. The number of asthma patients is increasing globally day by day. The Centres for Disease Control and Prevention (CDC) report showed an increased rate of asthma by 3.0% of the total U.S. population suffered from asthma in 1970, 5.5% in 1996, and 7.8% in 2006 to 2008 [58]. Considering the age of the patients, almost 18.7 million out of the 25.7 million asthma patients in the United States were adults (age of 3.1 million people were more than or equal to 65 years of age), and the rest 7 million were children in 2010. The global prevalence study of paediatric asthma is increasing very fast. According to a recent study of school children (7–10 years) in Poland, asthma prevalence in 1993 was 3.4% wherein in 2014, it reaches 12.6%. WHO reports also estimated global deaths of around 417,918 due to asthma in 2016 [58]. According to "The Global Asthma Report 2018", among 1.31 billion people, almost 6% of children and 2% of adults suffer from asthma in India [59]. A similar survey by WHO proclaimed that India is currently having approximately 15–20 million asthmatic patients and among them 10%–15% are children, which means every 3 people out of 100 are asthmatic in India.

The prevalence of asthma is also seen to vary between males and females. According to the studies, ascendance in the diagnosis of asthma in male patients just before their puberty has been observed, but in female patients, it is mostly found in adulthood. The CDC statistics (2008–2010) says that 9.2% of females and around 7% of males are affected with asthma, and it can differ in females and males, i.e. boys of age 0–17 years have a greater prevalence (11.1%) than girls (7.8%) but men of age 18 years or above have a lower prevalence (5.7%) than women (9.7%) [60]. Moreover, current CDC reports say that the black population has a higher abundance of asthma (11.2%) than the white population (7.7%). People of multiple races were seen to have the highest suffering (14.1%) with Asians being the lowest (5.2%). It has also been found that the prevalence of asthma is somewhat higher among the people of lower poverty line groups. Many otolaryngologic diseases like obstructive sleep apnoea (OSA), gastroesophageal reflux disease, allergic rhinitis, and chronic sinusitis with nasal polyposis; etc. are deeply related to asthma. For example; 40% of allergic rhinitis patients and 35.1% of patients having OSA have the prevalence of asthma [61].

4.2. Emergence of pediatric asthma

In infants and children, it is difficult to diagnose asthma. It is one of the most serious diseases in children. The most common symptoms that may appear are wheezing, rapid breathing, coughing, and deprived energy. The children whose parents have atopic diseases are more prone to suffer from asthma and the risk increases in the case of children having both parents with atopic history [62]. A string of atopic diagnoses initially starts with dermatitis and later impedes through allergic rhinitis and food allergies and ultimately ends with asthma. It has been found that almost 20% of the children with mild cases of atopic dermatitis and 60% of the children having severe symptoms of skin suffer from asthma. Aeroallergen sensitisation within 1 year of age of babies shows a high risk to have asthma. Dust mite hypersensitivity also increases the risk of childhood asthma. Bizzintino J. et al. found that infection with Human Rhinovirus (HRV) specially Rhinovirus-C plays an important role in developing asthma in paediatrics [63–65].

Another parameter can be exposure to microbiomes. Microbiome is the trillions of bacteria and other microbes colonising at the surface of the mucosa, which can also induce asthma and allergic disease [66]. In addition to atopy, the route of delivery of the baby also can affect the same. For example, the risk of developing asthma is greater in children delivered by the caesarean section in comparison to the children born by normal vaginal delivery, as the immune system of the children by caesarean section is generally disturbed due to the alteration of the microbial colonies. It was found that children living in the farming area have a reduced risk of having asthma. Moreover, a rural or less industrialized environment can improve lung function in both children as well as in adults [67].

4.3. Prevalence of Type-2 asthma in adults

Asthma that starts in adulthood is cursorily different from asthma in childhood. Adult patients may also have increased atopy like children. The most common causes that can influence adult asthma are:

1) Aspirin-Exacerbated Respiratory Disease (AERD) in which the patients can have symptoms like asthma, increased sensitivity to aspirin and other NSAIDs with sinus problems [68].
2) Obesity is broadly related to asthma and is more primarily observed in female patients. In the USA, about 60% of adults with asthma are obese. Not only the obese patients have a higher risk for asthma, but they also show reduced responses to systemic corticosteroids, given alone or in combination with long-acting β 2-agonists wherein the link between asthma and obesity is not well established [69]. From a meta-analysis involving 108,000 participants, it was found that maternal obesity or an increase in weight during pregnancy leads to a 15–30% rise in the risk of asthma to the offsprings [70]. Richard L. J. et al. studied the effect of body mass index (BMI) on lung volumes and found the exponential decrease in the functional residual capacity (FRC) and expiratory reserve volume (ERV) with the increase in BMI [71]. A similar study was conducted by Mehari A. et al. to analyse the relation between obesity and pulmonary function in African Americans, where the same conclusions were made about the decrease of FRC and ERV among the people having BMI values near to 30 kg/m^2. Inflammatory responses are common in both obesity and asthma. It has been seen that Classic TH2 inflammation is worsened in obese condition. The number of certain mediators like IL-6, IL-8, TNF-α, and many more are increased in obesity, which ultimately exacerbates asthma [72]. Yokoyama A. et al. found that IL-6 causes increased release of histamine, TNF-α, and IL-1 and IL-4 in the bronchial surface leading to bronchial asthma. Certain adipose-derived hormones like leptin and adiponectin are also involved in these phenomena [73].
3) Smoking and tobacco inhalation is a major consequence which may affect the airways by irritating the lining of the airways and damaging cilia, that is how it can trigger asthma. Passive smoking also causes reduced lung function and symptoms of airway inflammation. It has been observed that the mortality rate is more in the case of asthma patients who smoke and inhale tobacco in a daily manner [74].
4) Certain forms of asthma are seen due to the presence of allergens in particular environmental conditions or types of workplaces. The agents responsible for this include high-molecular-weight (HMW) compounds like wheat allergens, fungal enzymes; etc. and low-molecular-weight (LMW) compounds like diisocyanates. HMW compounds produce IgE dependent pulmonary, but LMW compounds cause asthmatic symptoms by non-IgE dependent mechanisms [75].
5) Asthma and COPD are the two most common and dangerous obstructive airway diseases. The patients having asthma-COPD overlap syndrome (ACOS) suffer from symptoms of both diseases, but more studies are necessary to find better diagnosis and treatment [76].
6) Hormonal factors may also affect puberty and may influence asthma. According to a study conducted among 16–18 and 19–24 years old females, 11% of them suffered from allergic rhinitis just after their first menstruation and 3% of them reported newly onset asthma. Besides that, girls having a late onset of menarche have less risk of allergic rhinitis after puberty compared to girls having menarche at

an average age. The use of hormonal contraceptives may protect women from asthma and some other allergies [77,78].

4.4. Pregnancy related factors

Maternal asthma is one of the major factors associated with developing early-life asthma. The study says that maternal asthma has an almost threefold greater risk of having asthma to the offsprings than those without maternal asthma. During pregnancy, maternal asthma control is another risk factor for asthma in offspring. Maternal vitamin-E (tocopherol) levels may affect lung foetal growth in early pregnancy. Decreased levels may reduce childhood lung function and increase asthma symptoms. Increased vitamin-D levels of pregnant mothers may reduce the risk of childhood asthma. Milk intake by the mother in the first trimester generally reduces the odds of childhood asthma and allergic rhinitis. Generally, children whose mothers are consuming antibiotics for non-respiratory infection, are observed to have a higher risk of asthma. The risk of antibiotic use mainly depends on the time. According to the study by Bai L. et al., antibiotic exposure during the last two trimesters of pregnancy can play a role to elevate the risk of childhood asthma [79,80].

5. Pathological cascades resulting in asthma

The pathogenesis of asthma has widely progressed in the past 30 years and the complex underlying concept is yet to unfold. Recently, the researchers remark that asthma is not a disease with single characteristics, rather it's a group of symptoms that are produced by one or more means [9]. Thus, there are various underlying factors and causes for the initiation of asthma. For the easy and fast treatment of asthma, several approaches are used to categorise asthma depending on their symptoms, intrinsic or extrinsic, genetic, or environmental factors. Medical professionals have classified asthma from mild to severe type depending on the symptoms like recent classifications of asthma are based on some observable characteristics including clinical characteristics, immunological condition, histopathology, lung physiology, symptoms, and response of patients towards appropriate treatment [9,81].

The normal respiratory epithelium plays a vital role in protecting the immunity of the lungs in several ways. The main shield is the ciliated respiratory epithelium covering the inner lining of the larynx, trachea, bronchi, and bronchioles which protects the respiratory tract against wide forms of allergens, dust, microbes, smokes and many more, preventing them from reaching the alveoli. Secretion of mucus from the tracheobronchial glands and goblet cells of the mucous membrane is another important mode to entrap the foreign particles and expelling out from the mouth or nose. Mucus keeps the respiratory tract hydrated and prevents the tract from drying [82,83].

A number of structural changes that occur in the airway are known as airway remodelling. In asthma, the abnormality in epithelium and submucosa is observed. Some changes in epithelium include non-cancerous changes and enlargement with a high level of mucin due to the increased reproduction rate of goblet cells. Changes in sub-mucosa include subepithelial fibrosis due to the deposition of collagen I, II, and V, along with fibronectin and tenascin-C; an increase in the size of sub-mucosal gland cell, smooth muscle cells, and an increase in the number of blood vessels also takes place [84]. This change occurs due to multiple inflammations along with the matrix protein and growth factor produced by the inflammatory cells. Airways are invaded by eosinophils, a type of disease-fighting white blood cells which often indicate a parasitic infection, mucus may contain many eosinophils with Charcot-Leyden crystals [6,85].

Extrinsic/Allergic/Atopic Asthma: This is one of the most common types of asthma usually initiated from the childhood or early adult phase. Majorly, it is genetic, which means the patients have a pre-existing family history of allergy conditions like urticaria, allergic rhinitis, or eczema. Hypersensitivity towards a variety of external agents is usually responsible for this problem. Increased serum IgE with positive skin tests against specific allergens represents the IgE mediated type 1 hypersensitivity reactions. It involves an acute immediate response and late-phase reactions:

The acute immediate response begins by IgE hyperactivity acting on the mast cells of the mucosal surface. Degranulation of mast cells releases several autacoids like histamine, platelet-activating factors, leukotrienes, prostaglandins, and many more that result in asthmatic attacks.

The late phase reactions are responsible for the extended exemplification of asthma. The main cause is due to increased blood leukocyte mobilisation which comprises basophils, eosinophils, and neutrophils that further releases other mediators to cause the attack [86].

Intrinsic/Idiosyncratic/Non-Atopic Asthma: This classification of asthma has delayed onset which initiates in the later phase in adult life with no family history of any allergies, normal IgE level, and negative skin test. The majority of the patients develop the symptoms following any viral infection that affects the upper respiratory tracts. Not such allergens are recognised in the patients by some who become hypersensitive to certain drugs including aspirin [83].

Mixed type asthma: The characteristics of some patients do not fit into any of the two above categories, but they have mixed features of both the characters. Asthma in initial life stages is mainly due to allergic predisposition whereas those who develop the disease later are non-allergic [23].

Type-2 asthma: Cellular inflammation in the lower respiratory tract arises from exposure to environmental allergens and may also be due to genetic susceptibilities. Most asthma is type-2 inflammation as there is an involvement of T helper cell type-2 lymphocytes (TH2 cell). Type-2 inflammation involves several cytokines like IL-4, IL-5, IL-9, IL-13, IL-14, mast cells, eosinophils, basophils, IgE, and type-2 helper lymphocytes which overall participate in different series of allergic bronchial inflammations. Among them, IL-13 is seen to directly act on the respiratory epithelial cells and smooth muscles, causing airway hyperreactivity, eosinophilia, and increased production of several glycoproteins [6,87]. Epithelial cells of the airways have also been reported to play a vital role in regulating type-2 inflammation via TSLP, IL-25, and IL-33. In the case of status asthmaticus, particularly in medium-sized bronchi, it is seen that the smooth muscle has thickened up to 2–3 folds. The thickening of the smooth muscles of the airways is directly proportional to aging in the case of asthma. It has been reported that accumulation of collagens and fibronectin (a high molecular weight (around 440 k Da) glycoprotein of the extra matrix which binds to integrins) is seen to be responsible for the thickening of smooth muscle and reticular basement membrane [33].

If we consider childhood type-2 immune responses, it initiates in the lungs on the exposure to the environmental stimuli such as pathogens like virus, bacteria, oxidants, smoke, or any other pollutants that again induces the production of TSLP, IL-25, or IL-33 from the epithelial cells of the airways and initiates the development of asthma in early ages. The reason behind the persistence of type-2 inflammation at an early age is yet not clear or maybe due to a weak immune system at an early age. Due to overexposure to some environmental stimuli at an early age, the immune cells can undergo an epigenetic change, which is a phenotypic change but not any change in the DNA sequence. The new method of classifying asthma is based on the symptoms triggered on exposure to particular allergens, by Skin Allergy Testing, a method to diagnose allergies that attempt to initiate a controlled allergic response or by measuring the specific level of IgE in the serum, which plays a vital role in initiating any allergic responses. The modern way of classifying the pathophysiology is based on the inflammation of certain cells, such as eosinophils and neutrophils, and their integration in the lungs of asthmatic patients. Some of the characteristics include- 1) Presence of eosinophils more than 1.9% but less than 2.5% in the sputum, bronchoalveolar lavage, or blood which may lead to eosinophilic asthma. 2) Presence of an increased amount of both eosinophils and

neutrophils that causes mixed eosinophilic and neutrophilic asthma. 3) Presence of neutrophils and eosinophils both within the normal range that causes paucigranulocytic asthma, and 4) Presence of neutrophils (>61%) and overall cell count greater than 10 million cells per gram causes neutrophilic asthma [20,33,88].

6. Risk of COVID-19 to asthma patients

The Coronavirus Disease (COVID-19) pandemic is a situation that has challenged the entire humankind. People throughout the world have a risk of being affected by COVID-19. People with older ages and patients with pre-existing medical history such as diabetes, severe asthma, heart diseases are more vulnerable to get affected by COVID-19. Though, it is considered that the patients with chronic asthma affected with the virus might have some worse outcome, but yet not such evidence is present to support this relation. However, in severe asthmatics, COVID-19 may cause a worsening of asthma symptoms as with other viral illnesses. The blood samples of COVID-19 positive patients have revealed increased levels of several cytokines like IL-1, IL-6, IL-12, TNF-α, IFN-γ; etc. which may have potential effects on lung inflammation and damage.

In host cells, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mainly cohere to Angiotensin-Converting Enzyme 2 (ACE2) receptors found in the heart, blood vessels, lungs, and intestine and thus mild to severe respiratory symptoms are mainly presented by COVID-19. A very significant number of patients present ARDS and thus the severe symptoms are related to a true hypercytokinaemia particularly IL-6, which could even be fatal [89].

Respiratory viruses most commonly trigger asthma even though the human rhinovirus has been identified as the main individual contributor in asthma exacerbations. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is also responsible for triggering asthma complications, asthma being a risk factor for COVID-19 morbidity. The most common symptom of COVID-19 is dry cough and shortness of breath which is also common with acute asthma exacerbation. Although fever is more correlated with COVID-19, it is also found in any infection-triggered exacerbation of asthma. Thus, it is suggested that anyone having to worsening of respiratory symptoms, even those including asthma should undergo screening protocols for COVID-19 [90].

As of April 15, 2020, 09:25 IST, Dr. Karan Madan, Associate Professor, Department of Pulmonary Medicine, AIIMS at ETHealthworld reported that all the patients with severe asthma are being treated with regular use of inhalers as the frontline management and considering biological agents/ drugs that are available like omalizumab, mepolizumab, resilizumab, benralizumab and dupilumab and other treatment options like Bronchial Thermoplasty (BT) as the two mainline treatments for severe asthmatics who are not in control despite initial treatment and In case any patient gets an acute attack, then that patient should be taken into the patient must consult their doctors if they notice any worsening of symptoms. All severe asthmatic patients are not required to regularly visit the hospital if their conditions are stable. Patients under the emergency criteria must be immediately taken to the hospital [91].

Apart from one's belief, patients suffering from asthma are not in the category of high risk for contracting the novel Coronavirus. Researchers of Rutgers University in New Jersey conducted a study and have found that non-asthmatics have no increased risk for acquiring COVID-19 as compared to asthmatic patients. Researchers have found a decreased level of T-cells in COVID-19, but the asthmatic patients suffering from COVID-19 have increased T-cell levels which seems to protect the patients from SARS-CoV-2 severity [92].

Bhatraju et al., from Seattle, USA, reported that 24 patients suffering from COVID-19 were warded to ICU, having 50% mortality rate. Among them, 14% were having a history of asthma, amongst them, 3 cases had mild asthma which were treated with glucocorticoids in the week prior to the admission to ICU, assuming to have an exacerbation of asthma. These patients were then immediately admitted to the ICU for having severe respiratory failure for which invasive mechanical ventilation has been essential [93].

Beurnie A. et al. performed a series of analyses from 15th March to 15th April 2020 at Bicêtre Hospital, University Paris-Saclay in France on all admitted patients having SARS-CoV-2 who also had a history of asthma. It was reported that 37 patients among 768 hospitalised patients had a history of asthma wherein 85% of cases were formerly established by a pulmonologist. Among these 37 patients, most of them were non-smokers (85%), and females (70%) with an average age of 54 years and 11 patients (30%) were GINA step 5, undergoing high doses of corticosteroids with beta 2-agonists. Initially, 50% of the patients had a peripheral oxygen saturation below 95% and 25% had a respiratory rate above 30 per minute. None of them was found with an asthma exacerbation. 22 of them had crucial comorbidities and 31 had a body mass index ≥ 25 kg m^{-2}, having the most familiar comorbidities found to be hypertension (27%), obesity (36%), and diabetes (19%). The chest computed tomography (CT) scan of all patients presented a confirmed diagnosis of COVID-19 pneumonia. Eosinopenia was seen to be a classical biological character. 11 patients were moved to the intensive care unit (ICU) and among which 3 deaths (8.1%) were seen in the account of comorbidities. Hence, this analysis focuses mainly on respiratory infections caused by the viral attack, which also includes other types of coronavirus as the main reason for asthma complications [94].

In the current situation amidst the pandemic, it is suggested to continue the same maintenance medications for asthma that physician has been prescribed. Moreover, scrutinizing appropriate inhaler technique, avoiding contact with aeroallergens, following regular hand hygiene, and maintaining physical distance are among other necessary precautions. It is also suggested to avoid nebulisation if feasible because nebulisation can expand the risk of aerosolization of SARS-CoV-2 infection transmission [90].

7. Management of COVID-19 in type-2 asthmatic patients

Type-2 inflammation is the common form of inflammation in asthma which is clinically associated with an increased blood eosinophil count (>300 cells per microliter), FeNO (>20 parts per billion), and sputum eosinophil count (>2%). The response in the lungs often start at a younger age, when the person comes in contact with viral infection affecting the respiratory tracts, or may arise due to smoking or other airborne pollutants, which can lead to the production of TSLP, IL-33, and IL-25 from the airway epithelial cells. All of them lead to bronchoconstriction, hyperaemia, mucosal oedema, viscid bronchial secretions, and damage to the bronchial epithelium, causing obstructions to airflow. Common symptoms of asthma patients in COVID-19 include fever with chills, drug cough, and shortness of breath with no nasal congestion, which distinguishes them from the patients suffering from allergies [83,95]. HRCT thorax scans of many patients revealed medial lobe and basal lobe consolidation with focal dilatation of bronchioles, suggesting a degrading effect on the lungs (Fig. 3).

Many patients with type-2 asthma who are suffering from COVID-19 develop acute respiratory disease syndrome (ARDS) due to the rise in IL-6 levels, which may even lead to death. This creates a big challenge for the medical staff to manage those patients. This creates a dilemma whether the proper therapy to control type-2 inflammation would be safe in the situation of COVID-19 or not. According to a study conducted in China, many people developed severe eosinopenia which could increase the severity of COVID-19. It still doesn't mean that treatments that reduce eosinophil count may become more vulnerable to COVID-19 [96]. Currently, the most preferred drugs in this scenario are omalizumab, benralizumab, mepolizumab, and dupilumab which targets type-2 inflammatory pathways and thus stabilise the patients from asthma attacks. Other strategies include the use of anti-IgE such as Omalizumab and anti-IL-4 or anti-IL13 have been shown to control the exacerbations. Certain clinical trials are also taking place to check the patients' condition by inhibiting IL-6 with Tocilizumab (NCT04306705;

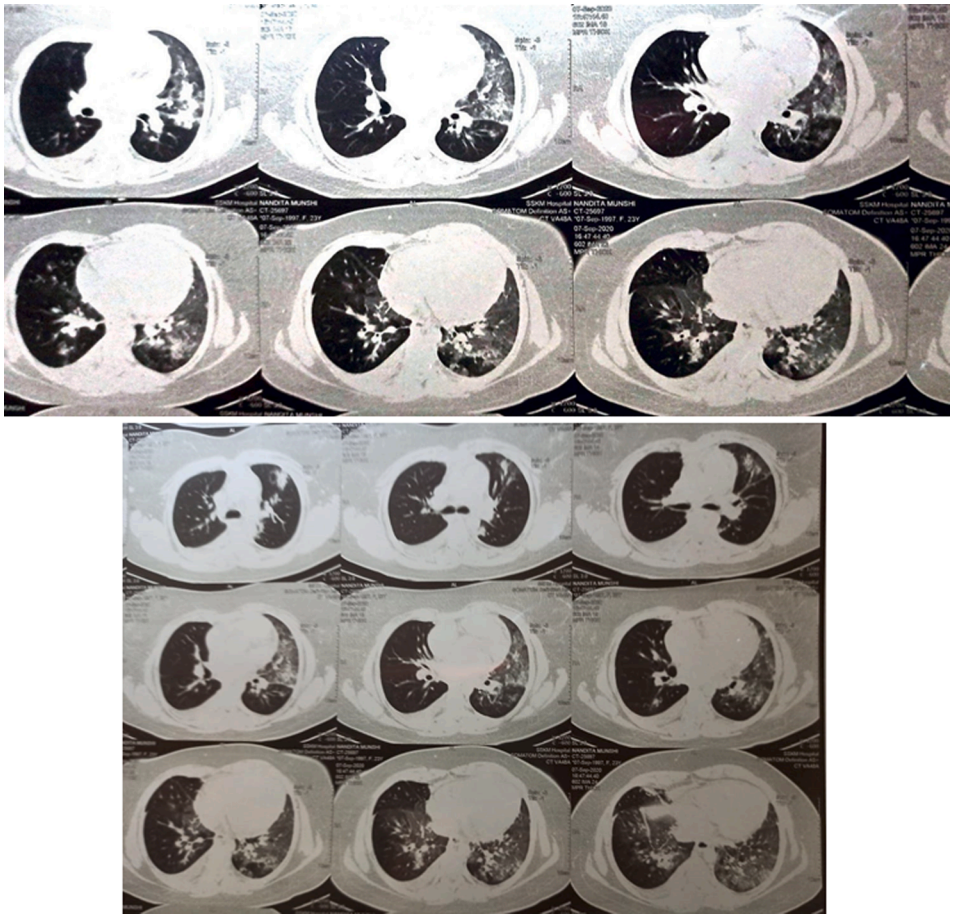

Fig. 3. HRCT chest scan of a COVID-19 positive 23 years old female patient. Complications including fever with progressive dry cough and shortness of breath were observed for seven days. The scan report is showing right lung medial lobe, left lung medial lobe, and basal lobe consolidation present, worsening with the course of time. Focal dilatation of bronchioles is suggestive of interstitial lung disease or bronchiectasis.

NCT04346355), Siltuximab (NCT04330638), or Clazakizumab (NCT04343989) [97,98].

7.1. Management of mild cases of COVID-19 with asthma

Asthmatic patients who have been confirmed to be infected with the virus should be isolated as early as possible to break the chain of spread. The patient must be quarantined in a separate room with proper ventilation of the room. Routine medical checkup must be performed to trace the patient's condition. Mild symptoms can be managed at local First Referral Units (FRUs), COVID Care Centre, or district/ local hospitals. Proper details of any disease or co-morbidities of the patient must be recorded. The temperature must be checked with proper oxygen saturation levels on a daily basis. Patients having any other risk factors must be handled carefully. In case of any severity, the patient must be immediately admitted to a nearby COVID hospital. The SPO_2 must be maintained at greater than 94%. In the case of fever, antipyretics like paracetamol should be given. Antitussives are given if required to counteract the dry cough. Proper nutritious food should be given to the patient and he/ she must be kept well hydrated. The patient should take appropriate inhalers as prescribed by the physician and should use emergency inhalers in case of shortness of breathing. Usually, beta-2 agonists like inhaled salbutamol are sufficient to counteract the attack. Anti-malarial drug, Hydroxychloroquine may be given as a prophylactic use to those patients having risk factors of other severe diseases or patients above 60 years of age (avoided if QTc is greater than 480 ms). Vitamin and zinc tablets can be given as a supplementary measure.

Healthcare personals including police or paramilitary who are in direct contact with the patients can be administered with Hydroxychloroquine as a prophylactic measure. A loading dose of 400 mg twice a day on day 1, followed by the maintenance dose of 400 mg once a week for 7 weeks is the official regimen that can be administered to them. Yet, it is contraindicated in children of less than 15 years of age, lactating women, and patients having cardiovascular problems. Fever is controlled by paracetamol.

An anti-influenzal drug, Favipiravir (Favilavir) is recently approved in India for its use in mild to moderate cases. It is a potent RNA-dependent RNA polymerase (RNA replicase) inhibitor with a special affinity for RNA virus. Favipiravir is given at 1800 mg twice on day 1 as a loading dose, then followed by 800 mg twice daily up to 7 days as a maintenance dose [99–101].

7.2. Management of moderate cases of COVID-19 with asthma

Confirmed COVID-19 patients with moderate symptoms like pneumonia and chest blockade should be isolated at first and must be transferred to a nearby emergency unit if worsening of consequences occur. Major clinical parameter checks should be done regularly including respiratory rate, which should not be less than 24 and oxygen saturation level (SpO_2) between 92 and 96%. Oxygen levels should be regularly checked with the help of pulse oximeters. Other inquiries like any history of co-morbidities, complete blood count (CBC) with the absolute lymphocyte count, KFT, LFT, X-ray of chest, checking vital symptoms, 12- lead ECG test, etc. must be carried out to correctly monitor the patient. Oxygen is given if SpO_2 falls below the normal

range. Antipyretics like paracetamol 500 mg is given thrice a day. Antitussive is given if required. Hydroxychloroquine is administered- 400 mg two times a day on 1st day, followed by 200 mg twice a day for 4 days after the proper ECG examination (Hydroxychloroquine is avoided if QTc is greater than 480 ms). A combination of beta 2 agonists along with steroids like salmeterol with fluticasone propionate, formoterol with budesonide; etc. are the best choices to prevent moderate asthmatic attacks. The use of leukotriene receptor antagonists like montelukast, zafirlukast along with 5-lipoxygenase (5-LOX) inhibitor like zileuton has also proven to decrease the risk of asthmatic exacerbation. In the case of increased inflammatory markers, intravenous administration of methylprednisolone is given at a dose of 0.5–1 mg/kg for 3 days. In secondary bacterial infection, antibiotics like Azithromycin tablet 500 mg once a day along with 1gm Ceftriaxone i.v. is given twice a day, every day for 5 days. Certain investigational drugs like Remdesivir or Tocilizumab may be given to the patients having moderate symptoms. Systemic steroids like dexamethasone (0.1–0.2 mg/kg) or methyl prednisolone (0.5–1 mg/kg) for 5 days is administered intravenously [99–101].

7.3. Management of severe cases of COVID-19 with asthma

Asthmatic patients with severe symptoms of COVID-19 can be quite risky and may need supportive intensive care. The patient must be immediately given oxygen to treat shock or hypoxaemia. Initially, oxygen at 5 L/min is given until SpO_2 reaches more than 92–96%. The children below 15 years of age are ventilated to maintain the SpO_2 of more than 94%. Different types of oxygen masks like simple face mask, nasal cannula, and mask having a reservoir bag should always be ready for the patients' requirement. When the patient is not responsive towards standard oxygen therapy, in that case, oxygen therapy is given via high flow nasal cannula (HFNC) and checked for any improvement within 1 h. HFNC delivers almost 100% heated and humidified oxygen having a flow rate of around 60 L/min. Fluid monitoring must be done regularly. Patients with ARDS should be ventilated for 16–18 h per day under constant medical surveillance. Azithromycin tablet 500 mg once a day along with 4.5 mg Piperacillin / Tazobactam i.v. is given 3 times a day, every day for 5 days in case of secondary bacterial infection. High doses of inhaled beta 2 agonists are given after 15–20 min for the initial hour, which can be continued up to 4 h. Anticoagulants like enoxaparin injection can be used if required. Medications like hydroxychloroquine can also be given in a dose of 400 mg bd for 1 day followed by 200 mg bd for 2 weeks. Antiviral drugs such as lopinavir 400 mg or ritonavir 100 mg bd are administered for the next 14 days. Immunomodulatory therapy with tocilizumab can also be done. Systemic steroids like dexamethasone (0.2–0.4 mg/kg) or methyl prednisolone (1–2 mg/kg) for 10 days is given intravenously. Remdesivir IV can be given to moderate to severe patients with a dose of 200 mg IV 1st day, following 100 mg IV for the next 5 days. In case of pneumonia, chest X-ray, sputum test, CBC, pleural fluid culture, SpO_2 must be checked regularly. Oral doxycycline tablet 200 mg on day 1, followed by 100 mg for the next 5 days may be used to control severe acquired pneumonia [99-101]. Detailed guidelines of treatment protocol according to the severity of COVID-19 symptoms are depicted in Table 1.

Table 1
Treatment protocol of different cases of COVID-19 in asthmatic patients.

MILD CASES	MODERATE CASES	SEVERE CASES
• To prevent attack: beta 2 agonists like inhaled salbutamol. • Supplementary Vitamin and Zinc tablets. • Anti-tussive if required	• Oxygen is given if SpO_2 falls below 92%. • Hydroxychloroquine: • Day 1–400 mg two times a day, Day 2 to day 6–200 mg twice a day. • Supplementary Vitamin and Zinc tablets. • Anti-tussive if required	• Initially, oxygen at 5 L/min is given until SpO_2 reaches more than 92–96%. Children below 15 years of age are ventilated in order to maintain the SpO_2 more than 94%. • Supplementary Vitamin and Zinc tablets. • Anti-tussive if required
• For Healthcare personals: Hydroxychloroquine (prophylactic measure) Day 1–400 mg two times a day Upto 7 weeks- 400 mg once a week. (Contraindicated to children of less than 15 years of age, to the lactating women and to the patients having cardiovascular problems.)	• To prevent moderate asthmatic attacks- Beta-2 agonists + corticosteroids like salmeterol + fluticasone propionate, or formoterol + budesonide; etc.	• After 15–20 min to 4 h: High doses of inhaled beta-2 agonists. • Hydroxychloroquine Day 1–400 mg bd Day 2 to 2 weeks: 400 mg
• For Fever: Antipyretics like paracetamol is given.	• For Fever: Antipyretics like paracetamol is given.	• Antiviral drugs such as Lopinavir or 100 mg bd ritonavir. • For Fever: paracetamol
• An anti-influenzal drug, Favipiravir: Day 1–1800 mg twice a dayday 2 to day 7–800 mg twice daily	• To decrease the risk of asthmatic exacerbation: Leukotriene receptor antagonist (like montelukast, zafirlukast) + 5-lipoxygenase inhibitor (like zileuton) • In case of increased inflammatory markers: Day 1 to day 3–0.5 to 1 mg/ kg methylprednisolone (IV) • For bacterial infection: Azithromycin 500 mg OD for 5 days, 1gm Ceftriaxone i.v. is given twice a day every day for 5 days • Investigational drugs like Remdesivir or Tocilizumab may be given for moderate symptoms.	• Day 1–200 mg Remdesivir IV Day 2 to day 5: 100 mg Remdesivir IV • To control severe acquired pneumonia: Day 1–200 mg Oral doxycycline tablet Day 2 to day 6–100 mg Oral doxycycline tablet • For bacterial infection: Azithromycin 500 mg OD for 5 days, 4.5 mg Piperacillin / Tazobactam i.v. is given 3 times a day every day for 5 days • Dexamethasone (0.2–0.4 mg/kg) or methyl prednisolone (1–2 mg/kg) for 10 days

7.4. Use of pulmonary surfactants

Pulmonary surfactant is a crucial lipid-protein complex that surrounds and stabilises the alveolar respiratory alliance, granting the exchange of gases during the cycle of breath. Surfactant present in the lung constitutes the first line of defence against various disease-causing pathogens and potentiate various other physiological functions. They bring about their function by reducing the stress at the air–water alliance. The surfactant present in the lung being synthesised by type-2 alveolar cells is a complex mixture of lipids and protein. They protect the lungs from collapsing. The lung surfactant is a complex blend of phospholipids and protein and comprises about 70–80% of phospholipid, mainly dipalmitoyl phosphatidylcholine (DPPC), 10% protein, and 10% neutral lipids consisting of cholesterol. The lung surfactant progresses up to the terminal airway and trims the production of liquid plug that can delay the way out airway at end-expiration. On the way to moving up the bronchial tree, the admixing of the lung surfactant with the airway mucus may develop fluidity wherein the cilia clears the mucus on the bronchus epithelium. Once in the airways, the surfactant enhances the clearance of inhaled particles and disease-causing pathogens from the alveoli, resulting in overall respiratory health. In the case of neonatal respiratory distress syndrome (NRDS), the amount of surfactant that is formed naturally is not up to the required level; therefore scopes of artificial surfactant replacement are possible and can be introduced in the endotracheal intubation. The most habitual clinically used natural surfactant for replacement are animal-derived. Natural

surfactants for replacement are obtained from the lungs of the minced cow with the addition of DPPC, tripalmitin, and palmitic acid. They can also be extracted from calf lung lavage fluid or lung of the minced pig [102–104].

Surfactants are generally composed of four associated proteins which are named surfactant protein SP-A/B/C/D. Among these proteins, SP-A and SP-D are lipophobic whereas SP-B and SP-C are lipophilic. The lipophobic protein, namely SP-A and SP-D belongs to the innate immune protein family and hence, they are termed as collectins. The most well-defined functions of the collectins are their capabilities to make cells more susceptible to the action of phagocytes and bring about phagocytosis by the cells of the innate immune system. The part common to this protein is the terminal NH_2 collagen-like region and a terminal– C lectin domain that helps in the binding of carbohydrates in a calcium-dependent manner. Viral and bacterial surfaces possess the lectin binding domain, which is another way responsible for the part collectins, helps in providing adaptive and innate immunity. The other two surfactant proteins, namely SP-B and SP-C are lipophilic which are stored and released with phospholipid. SP-B is a protein that not only plays a vital role in enhancing surface tension reduction but plays a major role in showing anti-microbial activity. The components of the surfactant are synthesised from type-2 alveolar cells which are responsible for the production of surfactant lipids and proteins [103,104].

The major functions being played by lung surfactants include bringing down the surface tension at the air–liquid interface, thereby preventing the collapse of the alveoli, killing any undesirable microorganism or pathogen and preventing their spread by managing the immune response.

During the respiratory cycle, radical changes take place in the surface area of the alveoli and the surface tension needs to less than 2 Mn/m to prevent alveolar collapse at the end-expiration [104]. To bring out and maintain this function of the surfactant, there is the presence of a film that is highly augmented by DPPC, which produces a surface tension of 1 Mn/M during compression. Surfactants also play a major role in the defence mechanism of the host against infections. They also bring about the production of cell-derived mediators. Discoveries made from a recent study elucidate that SP-A & SP-D have antimicrobial properties against Escherichia coli, Klebsiella pneumonia, and Enterobacter aerogenes and antifungal activity against Histoplasma capsulatum. SP-A1 & SP-A2 are the two genes that are found in humans and code for SP-A1 & SP-A2 protein. Apart from activating the immune system, the collectins also play their part as immunomodulators. Dendritic cell maturation and IL-8 release can be inhibited by SP-A. It has been found that SP-A & SP-D inhibit allergen-induced lymphocyte propagation. They also decrease allergen-induced histamine release by binding to particles such as house dust mite allergen, pollen grain, and many more [102,105].

Pulmonary surfactants provide a broad spectrum antimicrobial functions. SP-A & SP-D, the hydrophilic proteins, play a vital role in the host defence mechanism by inhibiting the growth of bacteria and promoting bacterial uptake by the host cell, assembling, and opsonising pathogens. These surfactant proteins have the ability to bind with both gram-negative and gram-positive bacteria. It can also bind to a number of fungi, which include opportunistic pathogens to bring about their commixture and phagocytosis by the host cell. Viruses are unique by nature and need to enter the host cell to replicate. As the collectins are present on the mucus layer and alveolar surface, they forbid the infection of the epithelial cell by the neutralisation of the virus and enhancement of phagocytosis. It has been observed that the collectins which are formed by SP-A and SP-D complex attach to the viral glycoprotein of several viruses like HIV, RSV, and even SARS-CoV-2. This creates a new scope of the treatment strategy to expel coronavirus from the respiratory tracts and limit the virus load [106,107].

7.5. Interleukin inhibitors

Some of the interleukins like IL-4 and IL-13 have been observed to amplify bronchial hyperresponsiveness by increasing mucous production and remodelling of the respiratory airway tract. Considering anti-IL-4/IL-13 biologics, a prominent functional similarity can be observed between IL-4 and IL-13 as they perform major roles by activating a heterodimeric receptor complex, which comprises IL-4Rα and the IL-13Rα1. These are targeted for asthma therapy. In COVID-19, there is an elevation in the level of certain interleukins that may be responsible to aggravate asthma. Hence, interleukin inhibitors can prove to be an advantageous therapy in that case. Other drug understudies include dupilumab, pitrakinra, altrakincept, pascolizumab, lebrikizumab, tralokinumab, etc. [22,108].

Dupilumab is a humanized monoclonal antibody administered subcutaneously acting against the alpha subunit of the IL-4 receptor and IL-13 receptors, thus disrupting their signalling pathways. It has been seen to improve FEV1 along with controlling type-2 driven persistent asthma in the patients having eosinophil levels of more or less than 300 cells/μL. It is also effective against nasal polyposis, atopic dermatitis, and chronic sinusitis [109,110].

Pitrakinra is an IL-4 mutein given via nebulisation, which is another IL-4α receptor inhibitor act by blocking the signalling pathway of IL-4 and IL-13. It is administered at a dose of 60 mg 2 times a day for 4 weeks to stabilize mild to moderate asthma [111].

Lebrikizumab is another subcutaneously administered, humanized IgG4 monoclonal antibody, which shows its affinity mainly towards IL-13 receptors. It is quite effective in uncontrolled type-2 asthma by improving FEV-1 but is ineffective in lowering asthmatic exacerbations. Unfortunately, its development is on pause [112].

Tralokinumab is another humanized monoclonal antibody developed by Astra Zeneca/Medimmune that is even more potent and specific to IL-13 and has a potential in the treatment of asthma. It is currently undergoing phase 3 clinical trials. [113].

IL-5 plays an important role in the development and release of eosinophils from bone marrow and increased adhesion to endothelial cells lining the postcapillary venules. This is the reason that IL-5 can be a better target to stabilise eosinophilic asthma. Some of the approved IL-5 inhibitors include mepolizumab, reslizumab, and benralizumab, which are usually prescribed to adults above 18 years of age. Mepolizumab is used to control mild to severe asthma. It has been shown to decrease the blood eosinophil count to a remarkable extent, but it is incapable to treat acute bronchospasm in case of status asthmaticus. Other uses of mepolizumab include Churg-Strauss syndrome, nasal polyposis, atopic dermatitis. Benralizumab is another class of humanized IgG1κ monoclonal antibody widely used in the treatment of asthma and COPD. It exerts its action by binding with the epitope of recombinant human IL-5 alpha at its Fab domain. Reslizumab is another class of humanized IgG4κ monoclonal antibody, assisting in inhibition of the activation and survival of eosinophils [114–117].

7.6. IgE inhibitors

IgE plays a crucial role in the pathogenesis of asthma with immediate hypersensitivity reactions like allergic asthma. It binds to Fc∈RI receptors with the high-affinity present over the mast cells and basophils, as well as binds to Fc∈RII receptors with low-affinity, which are present on B-cells, macrophages, and dendritic cells. Studies have determined the mechanism of cell activation through cross-linkage of IgE on mast cells and basophils which is involved in the dimerisation of Fc∈R1 receptors that leads to degranulation of lipid mediators that ultimately causes allergic responses, airway inflammation, and bronchoconstriction. Hence, by blocking the signal mediation of IgE, membrane-bound cross-linkage formation is interrupted that leads it to be a good target for asthma. Currently, IgE inhibitors like omalizumab, and ligelizumab are used in asthma treatment. Omalizumab is developed by recombinant DNA technology, which is a humanized IgG1 monoclonal antibody developed from the ovary cells of Chinese hamster. It is currently used in the treatment of persistent allergic asthma for patients

above 12 years of age. Ligelizumab (developed by Novartis), blocks the IgE/FcεRI pathway more effectively by binding to Cε3 domain of IgE and block it; hence used in the management of mild to moderate cases of asthma with chronic spontaneous urticaria [87,118–120].

7.7. Systemic corticosteroids (SCS)

SCS acts as an anti-inflammatory to the asthmatic airways where it inhibits the production of potent pro-inflammatory mediators and reduces the chemotaxis of inflammatory cells to the lungs. Sometimes, SCSs are prescribed as part of asthma self-management plans for patients at higher risk of exacerbations. Some common adverse effects of systemic corticosteroids include myocardial infarction, glaucoma, hypertension, hyperglycaemia, cataracts, depression, anxiety, and obesity. Long-acting SCS like dexamethasone has shown a great recovery rate in ventilated COVID-19 positive patients. According to Horby P. et al., a dose of 6 mg per day intravenous dexamethasone continued for 10 days or until discharged from the hospital has been shown to decrease the mortality rate by 35%. Due to severe adverse effects related to dexamethasone, patients must be monitored throughout the clock. Long term use of corticosteroids is prohibited as it may retard the clearance of the virus from the body. Other SCSs used in asthma include Intermediately acting prednisolone, methylprednisolone, or short-acting hydrocortisone [121–124].

8. Conclusion and future prospects

Gradually, asthma has become a significant domestic and global health issue. Majority of the population in India and Asia, remains undiagnosed and untreated. In that case, COVID-19 remains an extra burden to the people with type-2 allergic or eosinophilic asthma as there is a maximum chance of disease progression with a higher risk of secondary complications. The interferons elevated during COVID-19 infection may have a direct effect on the inflammation of respiratory tracts, thus aggravating the problem. Certain inflammatory cytokines like IL2, IL4, IL5, IL17, and other proinflammatory cytokines are elevated during the COVID-19 attack, resulting in massive cytokine storm or even pulmonary fibrosis with severe inflammation. All these events may exasperate bronchial asthma or COPD in those patients.

The fact that majority of the asthmatic population does not face any secondary complication or exacerbation due to COVID-19 and even recent research has found evidence against the protective action of type-2 asthma in COVID-19, controversially; still in some COVID-19 positive cases, crippled lungs with high oxygen demand were observed at the HRCT scan (Fig. 3) of the thorax due to bronchiectasis in the patients of asthma. This shows how dangerous viral infection can progress if not managed properly. Thus, more and more clinical and experimental research is required to gain knowledge about the exact relation between COVID-19 and asthma as the effect varies among patients. Management of COVID-19 patients having asthma requires special attention and must be transferred to nearby COVID-19 hospital in case of any complications. The treatment regimen is determined by analysing the severity of the disease. Patients with mild symptoms can be treated with home isolation. Regular use of prescribed inhalers and corticosteroids has been seen to a remarkable rate in stabilising the patient to normal. In case of severe complications like pulmonary fibrosis or pneumonia, corticosteroids like dexamethasone have proved like magic in disease control. Antagonising interleukins, especially by targeting IL-4, IL-5 and IL-13 can aid in curtailing hyperresponsiveness and excess mucous production during asthma attacks, thus assisting in disease modification. Many of the existing antiviral therapies which were earlier used for influenza or HIV are being examined to halt the disease progression. The use of pulmonary surfactants has also been seen to improve patients' compliance which is released by the alveolar type-2 cells of the lungs that were clinically seen to attach to the viral glycoprotein and also assists in minimising viral load in the body. Several vaccines are currently undergoing the race of clinical trials and the whole world is still awaiting a prominent cure for this pandemic. Numerous biological treatments are being developed via hybridoma techniques targeting different phenotypes and endotypes in asthma. Succeeding findings should also include better characterisation of the immunopathology of asthma exacerbation associated with COVID-19, including more studies and trials to explore better compounds as a potential target for asthma therapy. An increased amount of clinical surveys must be carried out to explore the effect of COVID-19 in asthmatic patients in the majority of the population and predict any possible aggravations that may happen due to this virus, which will enable us to treat the patients accordingly. Until then, asthmatic patients must remain careful and maintain suitable precautions in order to stay safe from COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to thank Guru Nanak Institute Of Pharmaceutical Science and Technology, West Bengal, India and Chitkara University, Punjab, India for providing immense support and to an intern of Medical College Kolkata, West Bengal for providing the HRCT thorax scan report.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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