International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 275-286 www.ijprajournal.com ISSN: 2456-4494

# Current Advances in Management of Respiratory Comorbidities: a focus on COVID-19 and Asthma

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Submitted: 01-11-2022 Accepted: 12-11-2022

**ABSTRACT:** COVID-19 is caused by the viral pathogen SARS-CoV-2. SARS-CoV-2 is a zoonotic pathogen that was transmitted to humans and caused severe respiratory infection. This review evaluated the management of SARS-CoV-2 infection among asthmatic individuals. The essence was to ensure that the comorbidities were effectively managed to prevent worsened outcomes. The studies included in the review revealed that the symptoms of both SARS-CoV-2 infection and asthma are alike. The pathophysiology of both diseases is somewhat similar. The pathophysiologic process involved in asthma can predispose asthmatic patients to infection with SARS-CoV-2 infection especially during a cytokine storm. Similarly, exacerbations of asthma can be triggered by SARS-CoV-2 pathophysiology. The management of both diseases are dependent on therapies that can effectively combat one of the diseases without triggering the other disease. Allergen immunotherapy, chloroquine and azithromycin were found in this review to be effective medications that reduced the predisposition of asthmatic patients to infection with SARS-CoV-2 as well as prevented the development of an asthma attack in the presence of SARS-CoV-2 infection. This study recommends that the effective medications should be employed in future treatment needs to reduce mortality, in addition studies should be carried out for the development of novel medications that can combat respiratory comorbidities of asthma.

**Key words**: Asthmatics, comorbidities, Healthcare, Pandemic, Proinflammatory.

## I. INTRODUCTION

The Coronavirus disease 2019 (CoVID-19) remains the most recent pandemic, especially in the line of pandemics affecting the respiratory tract. The viral pathogen,severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged as a pathogen of public health concern. Presently, the record shows that no less than 320 million people residing in 213 countries have been infected by SARS-CoV-2, and among them the mortality toll is over 5.5 million persons[1]. SARS-CoV-2 is a zoonotic pathogen, the animals that serve as a reservoir have remained a major source of first contact with humans, and among human-to-human transmission cases; saliva, phlegm and other bodily fluids have played a crucial role. Evidence has identified the respiratory system of humans as the main point of infestation in addition to muti-organ infection that can result in multi-organ failure. An interesting point to note in the pathogenesis of SARS-CoV-2 is that it results in high production and concentration of proinflammatory cytokines in the plasma as well as a rise in the leukocyte population[2]. This condition can exacerbate pre-existing co-morbidities such as those that are already affecting the respiratory system, example chronic obstructive pulmonary disease (COPD) and asthma in addition to cardiovascular diseases, diabetes and rheumatic diseases[1]. It is important to note that underlying health conditions do not predispose patients to getting infected, however, the conditions may simply be worsened once SARS-CoV-2 is involved especially among individuals who have an underlying respiratory tract disease. Tabassum et al. [3], had reviewed the incidences of asthma and SARS-CoV-2 infection, they highlighted the pathological involvements of asthma and suggested the possible options for management of both asthma and SARS-CoV-2 infection. Tabassum et al. [3], Bakakos et al. [4]) also reviewed the involvement of SARS-CoV-2 and asthma in context. Both studies made commitments to discussing the treatments for asthma and SARS-CoV-2, however this is the first study that is intent on reviewing the management of SARS-CoV-2 in asthma. The review begins by discussing the clinical features of both SARS-CoV-2 and asthma as well as their overlapping features. The review further presents details about the pathophysiology of both SARS-CoV-2 and asthma, it then highlights the possible exacerbation of asthma by SARS-CoV-2 infection. Finally, the review discusses the options for management of the

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 275-286 www.ijprajournal.com ISSN: 2456-4494

occurrence of SARS-CoV-2 among asthma patients with a keen focus on highlighting the best options. This study can underpin future observational, experimental studies in relation to management of respiratory virus infections in asthmatic individuals.

**SARS-COV-2 INFECTION AMONG PATIENTS: CLINICAL FEATURES**

The symptoms and prognosis of SARS-CoV-2 infection among people who are asthmatic is warranting of attention.

Briefly, the early signs and symptoms of SARS-CoV-2 prognosis show that within the first four (4) days of infection, the individual is likely to present with increases in body temperature that exceeds 100$^{o}$F. this occurs in conjunction with dypsnea and the infected individual may experience myalgia, sustained fatigue, sore throat and runny nose[5]. After the first four days, over the next four days (days 5 to 8), the infected individual may experience severe dypsnea and it is worse among the elderly who already have an underlying health condition, both soreness of the throat and constant runny nose are the main clinical features of this stage – consequent to this, the patient may have to be hospitalized[6, 7]. After the first eight days have elapsed, between days nine to fourteen, the patients may experience silent hypoxia, this can lead to acute respiratory distress syndrome (ARDS) that causes severe lung damage. Other symptoms at this stage include pain in the abdomen, and anorexia, at this stage it is imperative that the patient be admitted into the intensive care unit, other likely symptoms include diarrhoea and sustained dypsnea[8].

**ASTHMA AND ITS CLINICAL FEATURES**

Asthma is a non-communicable disease characterized by several complexities. Several genetic and environmental factors can cause asthma as well as the nature of occupation. Its pathological signs id the sever inflammation that causes the narrowing of the air passages[9,10]. This is because the air passages are highly sensitive to triggers within the environment, in addition to resulting in severe mucus production and dypsnea that is due to airway obstruction. Asthma flare-up or attack may ensue if an asthmatic patient faces any form of challenges in the airway [11]. Asthma attack is characterized by wheezing, intensive coughing, dypsnea and angina. A complexing aspect of asthma is that it demonstrates several features clinically, these features may result from the effect of several biological (sex, and age) and demographic (race and socioeconomic status) features as well as the nature of the environment[12]. The World health Organization highlighted the fundamental symptoms of asthma and they include the frequent breathless events, insomnia, wheezing, fatigue and reduction in activity[1]. The severity and susceptibility of asthma is associated with multiple epigenetic considerations and findings have revealed that the prevalence is high among people who less than fourteen (14) years of age. Asthma is classified based on its severity into mild, intermittent, mild-persistent and severe persistent, all four stages are characterized by a consistent reduction in respiration rate and functioning of the lung[13].

**OVERLAPPING FEATURES OF SARS-COV-2 AND ASTHMA**

Infection with SARS-CoV-2 has distinct features, however some of the features are also similar to the features of asthma. This understanding is important to ensure good measure of differentiation. Coughing, dypsnea, and fatigue are the main overlapping symptoms[14]. This is primarily because both diseases affect the respiratory system. Other symptoms such as myalgia, headache, diarrhea, prolonged fever and loss of sense of taste are typically associated with SARS-CoV-2 infection but not asthma. In contrast asthma is rife with wheezing. The features of SARS-CoV-2 and asthma can be found on Table 3.

**PATHOPHYSIOLOGY OF SARS-COV-2**

The pathophysiological features of SARS-CoV-2 infection involves the main stages of viral replication. It begins with attachment to the cells of the host, followed by penetration and a biosynthetic phase in which the virus replicates itself by using the host cell machinery, afterwards the virus maters and through lysis it is released[15]. The main enzyme that enables the entry of SARS-CoV-2 into the host cell is the angiotensin-converting enzyme-2 (ACE-2) receptors. ACE-2 is expressed prominently within the apical mucosal membranes that are found within the vital organs such as the lungs, the heart, kidney, ileum, small intestine and the bladder [16]. Apparently, the ACE-2 receptors function attachment points for SARS-CoV-2 and it has a predilection for the ACE-2 receptors that are found within the respiratory tract. It achieves its attack by using the spike protein and it is capable of invading other cells of the host, this can result to multi-organ damage. The presence of cleavage site in the S-protein of SARS-CoV-2 gives it high affinity for ACE-2 receptors in contrast to the low affinity associated with SARS-CoV[17]. Findings

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have implied the presence of an interaction with CD147 a glycoprotein located at the transmembrane. CD147 is commonly expressed in tumor tissues and cells that are infected with pathogens – this was recognized as a route of infection for SARS-CoV-2. Upon release of its RNA genome into the cytoplasm of the host, the double stranded RNA results in an immune response by initiating the activity of toll-like receptors (TLR), namely; TLR-3 which is responsible for the stimulation of interferon (IFN) type 1 through signalling pathway cascades, this process promotes the expression of IFN-stimulated genes (IFGs). Another TLR that is activated is TLR-4. TLR-4 activates pro-inflammatorycytokines and causes the recruitment of immune cells to the infection sire[18]. The T cells are presented with the antigenic parts of SARS-CoV-2 consequent to its digestion. The T cells which are secondary immune cells begin to proliferate, this is because of the demand for viral clearance, but this can result in a cytokine storm[19,20].

Studies carried out on patients experiencing severe COVID-19 revealed that the main mechanism of the cytokine storms are dependent on the high concentration levels of interleukin (IL)-1β[18]. Other interleukins involved are the IL-1Rα, and IL-7, to IL-10a. in addition, IFN-γ, interferon-γ-inducible protein (IP-10), basic fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), monocyte chemo-attractant protein (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1α), and (MIP-1β), tumor necrosis factor (TNF- α), platelet-derived growth factor (PDGF), and the vascular endothelial growth factor (VEGF)[21].

Patients who are experience severe infection with SARS-CoV-2 have demonstrated deficiency in levels of natural killer (NK) cells, as well as memory T cells, regulatory T cells (Treg Cells), as well as thrombocytopenia and lymphocytopenia. The impairment in the immune response is indicated by the atrophy of the lymph node and the spleen. These severe damage to the immune system may be as a result of direct attack by the virus or due to the cytokine storm. However, direct attack by the virus is believed to be the cause because the number of ACE-2 receptors declines significantly among dendritic cells of the alveolar macrophages[22].

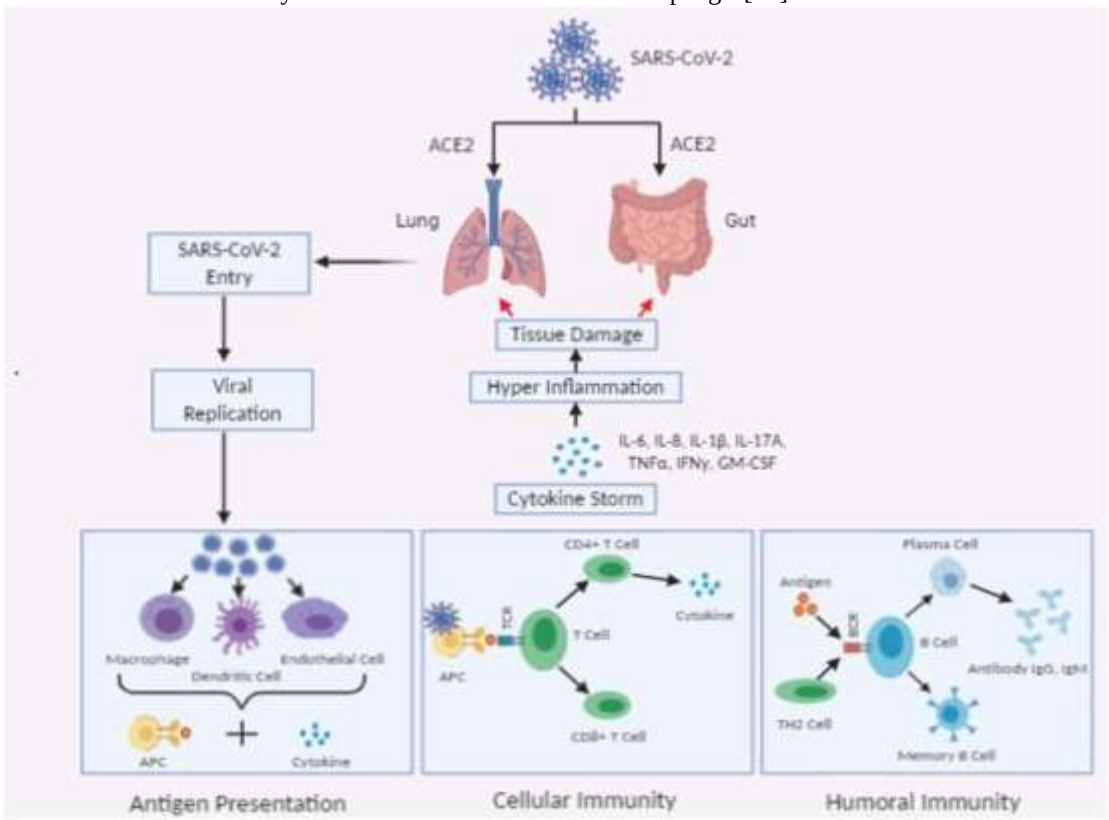


**Figure 1**. The Pathophysiology of SARS-CoV-2[23]

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## THE PATHOPHYSIOLOGY OF ASTHMA

The advent and implementation novel molecular and biological techniques enabled the evaluation of phenotypic features as well as the complexities involved in the interaction between asthmatic pathways. These novel technologies revealed a variety of factors that are associated with airflow limitation. Constriction of the bronchi is a popular feature in asthma and it leads to airway narrowing. Immunoglobulin E (IgE) which is associated with allergy, responds to the stimulation from both irritants and allergens alike. This mediates histamine release as well as the release of tryptase, leukotrienes and prostaglandins that are involved in the constriction of the bronchi[24].

Nonsteroidal anti-inflammatory medications can also provoke the release of mediators that result in the constriction of the bronchi[1]. Both IgE-dependent and non-IgE-dependent pathway mechanisms are involved in the underlying inflammation.Asthma is usually mediated by responses initiated by type-2 immune cells which are comprised of the type-2 B cells, group 2 innate lymphoid cells, the T-helper cells, eosinophils and basophils, and mast cells. Findings have highlighted the massive expression of TH2 cytokine among asthmatic patients which is capable of explaining the excessive production of high-affinity IgE molecules, eosinophils, increased airway hyperresponsiveness, increase in NK cells and a subsequent decline in the concentration of Treg cells[21].

The presence of allergens have been found to activate the mast cells of the mucosal membrane. These mas cells are responsible for cytokine release as well as the release of other mediators that are involved in the promotion of inflammation and acute bronchospasm[10]. The high concentration of eosinophils has been correlated with the severity of the condition, as the eosinophils release an expansive range of proinflammatory cytokines and inflammatory enzymes. Investigative studies on the involvement of eosinophils in asthma have been conducted, in one study using an anti-IL-5 therapy to limitthe production of eosinophils within the air tract, the reduction was not achieved and the disease persisted[9,10].

The involvement of neutrophils in the airways of the asthmatic patients is such that the concentration increases, however not much information is available as regards their pathophysiological involvement. All the inflammatory cells as well as the mediators such as the cytokines and chemokines impact negatively on the smooth muscles of the airways and can exacerbate the severity of the condition thus leading to dysfunction of the airway and causing the formation of obstructive lesions and injuries[14].Increased secretion of mucus is one of the main outcomes of worsened inflammation in addition to oedema and inspissated plugs whose formations result in airway smooth muscle hyperplasia and airway remodelling. This reduces the sensitivity of the individual to medications administered. These types of physiological changes cause the frequently observed wheezing, persistent dry cough and dypsnea[25].

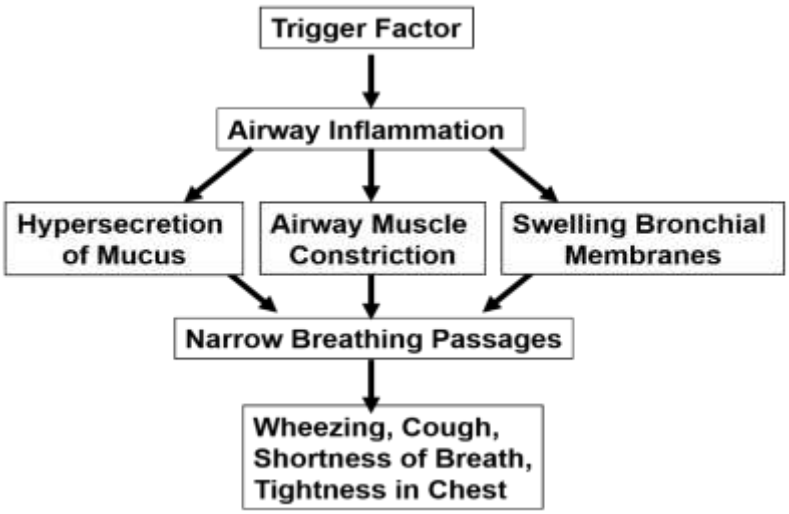


**Figure 2**. The Pathophysiology of Asthma[26]

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## PREVALENCE OF COINFECTION WITH ASTHMA AND SARS-COV-2

Several studies were carried out on the prevalence of SARS-CoV-2 infection among asthmatic patients. The centres for disease and control (CDC) claims that people who have asthma may face the worst of outcomes if they are infected with SARS-CoV-2 (CDC, 2019). The findings from the UK-Biobank study revealed that estimates of the non-allergic asthma can result in a 48% increased risk of getting SARS-CoV-2 infection. An observational study carried out by[27] revealed that 14% of a total of 16,749 patients had both asthma and SARS-CoV-2 infection. Similarly, [28], revealed from their prospective cohor studies carried out in England that asthma is highly likely to increase the risk of mortality from SARS-CoV-2 infection. A study carried out by the CDC among patients who were hospitalized in the USA revealed a 27.3% prevalence of comorbidity with both asthma and SARS-CoV-2[29]. A 12.9% prevalence of SARS-CoV-2 infection was obtained among elderly people who were hospitalized [29]. It is confirmed that people who are aged between 18 years and 49 years are highly likely to present with asthma may also become infected with SARS-CoV-2[30]. Among children infection is rare nut asthma may be exacerbated in the presence of SARS-CoV-2 [29, 30]. Bhataraju et al., [31] found that among people living in the USA, 1 in 8 persons who are critically ill with SARS-CoV-2 already have asthma.

Studies such as those carried out by Reflecting on world asthma day, [33] have revealed contrasting evidence that debunks the claims that asthmatics are at increased risk of getting infected with SARS-CoV-2. Specifically, Reflecting on world asthma day, [33] claimed that in USA and China, there is a reduced prevalence of SARS-CoV-2 occuring among asthmatics. Similar to Reflecting on world asthma day, [33],Korean Society of Infectious Diseases, [34] claimed that in Korea there is no comorbidity between asthma and SARS-CoV-2 infection. Among 552 hospitals in 30 Chinese provinces, Guan et al. [35] revealed that SARS-CoV-2 did not occur in asthmatics. A cohort study conducted byChhiba et al. [36] also showed that only 0.9% of the patients infected with SARS-CoV-2 had asthma.

Asthma is not recognized in the top ten health conditions that can present in SARS-CoV-2 infection.

Findings obtained by Sunjaya et al. [37], revealed an 8.08% pooled prevalence of SARS-CoV-2 among asthmatic patients. Lee et al. [38], also found that out of 686 asthmatic patients who had SARS-CoV-2 infection, there was no significant relationship between the infection and respiratory failure or mortality. Lombardi et al. [39], identified that people who are elderly and people who have underlying health conditions are highly likely to experience the worst otucoems of SARS-CoV-2 infection. A study by Shi et al. [40], showed that there was a 7.0% prevalence of SARS-CoV-2 among asthmatics in Scotland. The study carried out by Philip et al, [41], revealed that out of 4500 participants who had asthma there was a 10% prevalence of SARS-CoV-2 infection. According to the study by [12], asthma patients who had SARS-CoV-2 infection had severe comorbidities such as cardiovascular diseases, obesity and diabetes. Habernau Mena et al. [42], diagnosed SARS-CoV-2 infection in 201 asthmatic patients. The findings of Morais-Almeida et al. [43], stated that respiratory virus tend to exacerbate asthma, and that there is insufficient evidence to support the fact that asthmatics are at a higher risk of severe illness.According to Liu et al. [19], they found that there was no significant association in the prevalence of asthma between patients who were hospitalized for SARS-CoV-2 infection and non-hospitalized patients. Based on the findings of Kim et al. [44], asthma morbidity was a major risk factor for severe SARS-CoV-2 infection. They added that patients who presented with recent exacerbations of asthma showed higher severity of SARS-CoV-2. Luo et al. [45], identified 16 patients who had asthma and were infected with SARS-CoV-2 and the mortality rate was 12.5%, however, there was no statistically significant difference in the mortality rates between asthmatic and non-asthmatic patients who were infected with SARS-CoV-2.

## MANAGEMENT OF ASTHMA IN SARS-COV-2 INFECTION

### A. Nebulizer and Inhaler

The underpinnings of nebulization therapy is that active ingredients of a medication are transported as droplets or mists to the active site within the lung [46]. As beneficial as this form of therapy is, it is disadvantaged by the fact that some portion of the ejected mist may return into the tube, this is capable of increasing risk of infection with SARS-CoV-2 [47]. The chances of infection are higher if the nebulizer was used by an individual who is infected with SARS-CoV-2. The aerosol from the nebulizer has been confirmed to persist in the air for up to an hour[46], this can increase the likelihood of infection. According to NICE (the

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National Institute for health and Care Excellence), the fluid within the nebulizer is unlikely to contain any viral particles, notwithstanding this, it is recommended that alternative methods example the metered-dose inhalers (MDI), spacers or the dry powder inhalers (DPIs)[48].

**B. Inhaled Corticosteroids (ICS)**

These are regarded as the most effective and comprehensive medicines for the management of asthma. Even in reduced doses, the inflammation can be suppressed using this drug as well as the management of lung injury arising from inflammation (Global Initiative for Asthma, n.d.). However, the use of ICS is complexed because Global Initiative for Asthma, (n.d.), found that ICS can control viruses while[49], found that ICS can cause pneumonia, alter the nasal microbiota andprolonging of viral clearance. ICS is highly beneficial with some contrasting findings. It was identified byYamaya et al. [50]; Matsuyama et al. [51], to be effective in the pre-treatment of epithelial cells of the human respiratory system when combined with agents such as formoterol, glycopyrronium and budesonide which are capable of preventing the replication of SARS-CoV-2. Peters et al. [52], identified that using ICS can effectively control the expression of ACE-2 and the transmembrane protease serine 2 enzyme in sputum.

**C. Oral Corticosteroids (OCs)**

The use of OCs can exacerbate the vitality of the infecting respiratory virus. Key events include prolonging viral replication and complexing the clearance of the virus, these in addition to increasing the risks of ventilation as well as induce secondary infections that can influence mortality rates negatively. Common corticosteroids include prednisolone which is commonly used for management of asthma and has not been implicated in the challenges that OCs creates. Hence it is suggested that asthmatics can use prednisolone if they have not presented with SARS-CoV-2 infection. Licksai et al. [53], stated that using prednisolone in the presence of SARS-CoV-2 can worsen the outcomes. Another remarkable corticosteroid is dexamethasone which is used for asthma and has been confirmed to be effective in SARS-CoV-2 patients[54].

**D. Biopharmaceutical Agents**

The use of biologic medications such as anti-IgE and anti-IL5 monoclonal antibodies are highly effective in the reduction of asthmatic exacerbations.Licksai et al. [53], noted that there were no impairments of the immune system and the risk of viral infections was not increased. Using anti-IgE and anti-IL5 can protect asthmatic patients from viral exacerbations[55].According to the findings ofEsquivel et al. [55], blockage of IgE is essential for reducing viral infections, this is because IgE is involved in weakening of the immune response to viral infections especially among asthma patients. Anti-IgE medications are capable of upregulating the signalling of interferon-α, in the dendritic cells as well as reduction in viral infection.

**E. Allergen Immunotherapy**

Allergen immunotherapy is considered as one of the most effective approaches for personalized medicines for allergic diseases[56]. It can modify the responses of the immune system by altering the spectrum of IgE. According to Passalacaqua and Canonica, [57], allergen immunotherapy has long-term effect and it can modify the responses of T and B cells. Treg cells can release inhibitory cytokines which are involved in the suppression of TH2 responses, as well as being able to play an essential role in the control of cytokine storm, inflammation and prevention of damage to the tissues of the lung [58].

**MANAGEMENT OF SARS-COV-2 AMONG ASTHMATICS**

Through investigational therapy during the SARS-CoV-2 pandemic, medications for the management of SARS-CoV-2 infection were identified.

**A. Remdesivir**

One of the most frequently used medications was remdesivir which acts by inhibiting viral RNA-dependent RNA polymerase [59, 60,61]. According to Beigel et al. [61], clinical trials conducted to evaluate the effectiveness of remdesivir revealed a shorter recovery time among SARS-CoV-2 patients who were hospitalized and the difference was significant when compared to the placebo group [61]. The drug is considered ineffective against asthma due to its mechanism of action[62].

**B. Chloroquine**

Chloroquine and its derivative hydroxychloroquine are capable of inhibiting the glycosylation of ACE-2 receptor as well as being able to interrupt the attachment of SARS-CoV-2 to the cells of the host. Both chloroquine and hydroxychloroquine are capable of raising the pH

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of the endosome with the intent of inhibiting the fusion process between viruses and the membranes of the hosts cell. The medications can also block the transportation of SARS-CoV-2 from early endosomes to the endolysosomes thus preventing the release of the viral genome [63,64]. Being that both chloroquine and hydroxychloroquine possess anti-inflammatory activity, they can be effective among asthma patients. Chloroquine is commonly used in asthma treatment as a steroid-sparing agent. Ensuing controversies exist in relation to the toxicity of the medicines and their antiviral activity [65].

### C. Azithromycin

The anti-inflammatory medication azithromycin was evaluated byGautret et al. [66], for its anti-SARS-CoV-2 activity. Azithromycin possesses immunomodulatory properties that are involved in the downregulation of cytokine production. The medication is also involved in the maintenance of the integrity of epithelial cells and can prevent the damage of the lungs during infection with SARS-CoV-2. Echeverria-Esnal et al. [67], noted that azithromycin is involved in the management of mortality rate due to SARS-CoV-2 as well as reduction in its severity. Azithromycin is also considered to be effective for treating asthma considering that it has immunomodulatory potentials.

### VACCINES AGAINST SARS-COV-2

The prevalence of allergic reactions due to COVID-19 vaccines are considerably low and no findings have been published supporting the claim that asthmatics are likely to suffer the most allergic reactions. According toCagigi et al. [68], there is a possibility that SARS-CoV-2 mRNA vaccines can result in the production of IFN-1.Baraldo et al. [69], noted that IFN-1 has been produced excessively during viral induced exacerbations of asthma. This indicates that mRNA vaccines can have a negative impact on asthma patients.

## II. SUMMARY

The fact remains that respiratory diseases be they of infectious or non-infectious origin are of serious concern in medicine and healthcare. This is because respiratory diseases are life threatening and can impact on virtually every aspect of an affected individual in addition to causing related comorbidities. It is important to recognize the impetuous role of SARS-CoV-2 in healthcare. It was a devastating viral pathogen that left several victims in its wake and even with the current declaration of the end of the pandemic, SARS-CoV-2 like its predecessor (SARS-CoV) remains a viral pathogen of significant attention. The pathophysiological processes involved in the progression of SARS-CoV-2 infection is one of the main challenges. The pathophysiology of SARS-CoV-2 infection is somewhat similar to the pathophysiology of asthma and both asthma and SARS-CoV-2 present with similar symptoms. A key point to note is that the proinflammatory processes of asthma enables the possibility of asthmatics acquiring infections of all kinds, especially viral infections since IgE is significantly suppressed. The choice of medications is crucial to ensure that asthmatic patients do not come down with microbial pathogenic infections such as SARS-CoV-2. This is why oral corticosteroids are no longer advisable for treatment of asthma. Rather attention is now given to allergen immunotherapy, chloroquine and azithromycin.

## III. CONCLUSION

The management of SARS-CoV-2 infection and asthma are crucial because they are diseases that involve the respiratory tract which means they can be life threatening. This review established the importance of employing allergen therapy, chloroquine and hydroxychloroquine and azithromycin in the management of comorbidity of SARS-CoV-2 and asthma.

## IV. FUTURE WORK

SARS-CoV-2 is now in the history books as a severe respiratory infection that is warranting of attention. However, the possibility of similar viral infections re-emerging in the future does exist. The world ought to simply prepare through research and development to formulate medicines and vaccines that can fight viral respiratory infections. This is important because being caught unaware was one of the major challenges associated with the death toll of SARS-CoV-2. Especially for individuals with underlying health conditions that can be exacerbated by such infections as well as underlying health conditions that could exacerbate such viral infections. As an instance the management of SARS-CoV-2 in asthma can be considered a critical instance of two respiratory diseases of infectious and non-infectious origin. The level of attention that should be given to the management of such disease should be based on perspectives that curtail exacerbations of the diseases.

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Volume 7, Issue 6 Nov-Dec 2022, pp: 275-286 www.ijprajournal.com ISSN: 2456-4494

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