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PATHOPHYSIOLOGY, RISK ASSESSMENT, AND MANAGEMENT FOR ASTHMA PATIENTS DURING THE COVID-19 PANDEMIC OUTBREAK

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ABSTRACT

Innumerable personages are associated with susceptibility to the COVID-19 pandemic viral infection evolution, which has globally overblown the healthcare facilities. Following the emergence of respiratory syndrome coronavirus, 2019-nCoV delineates as a third major emergence of a novel coronavirus. β-coronavirus having suspected origin from bat comprehend congestion of the respiratory system, indicating a worldwide life threat to around 235 million asthma patients' existents as per WHO records. This review aims to investigate the risk constituents involved in virus-induced asthma, its management and prevention, origin, and transmission of coronavirus, including the relationship between different CoV infections. This review culminated the role of cytokines and chemokines and others found in COVID-19 patients, which could directly or indirectly affect the smooth muscle contractility reasoned to promote asthma severity, but this still remains unknown. The research highlights how essential it is to regularly wash your hands and clean surfaces that are touched by your hands in order to prevent illness. Some pre-clinical data suggests the preferred use of a PDE4 inhibitor like Roflumilast in case of uncontrolled virus-induced asthma exacerbations. Although there is a lack of particular asthma management so far, that is why the rectification of the consequences can only be done by taking supportive treatment.

Keywords: Covid-19; Coronavirus; Asthma; Risk Assessment; Virus-Induced Asthma; PDE-Inhibitor.
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INTRODUCTION

The 2019 coronavirus pandemic has scared the bejesus out of the globe, but for those with asthma, this could be more assailable. As β genus subgenus *sarbecovirus*, *Orthocoronavirinae* subfamily[1], 2019-nCoV is associated with tiredness, fever, breathlessness, dry cough, and other symptoms of the respiratory symptoms, and asthma itself is comprehensively characterized by hyperreactivity, repeated episodes of wheezing, coughing, or chest congestion. Regulatory and statutory bodies like the Centers for Disease Control and Prevention (CDC), The Asthma Society of Ireland have frightened the world by including asthma as one of the risk factors, alongside diabetes and heart disease, that can pose potential risks to individuals.[2,3] To begin with, since the 12th century, the correlation between the common cold and respiratory tract infection has been going on.[4] Among these major erstwhile investigations of the total asthma exacerbation cases are associated with viral infections.[5] There are reports showing respiratory tract viral infections such as influenza, coronavirus, and adenovirus have the tendency to attack those already suffering from asthma or other respiratory congestion diseases.[6] Whilom research has also ventilated about the correlation between viral infections, immune response, and allergy and asthma.[7] Other viruses that induce asthma exacerbation are parainfluenza 3 virus, respiratory syncytial virus type A and B, enterovirus, bocavirus, and many more.[8,9] Comprehensively, it is aforesaid that allergy may augment the exposure of a person already suffering from allergic diseases to virus infection. Because they work together to exacerbate allergic illnesses caused by allergens and viruses, especially respiratory allergies.[10] This review aims to investigate the risk constituents involved in virus-induced asthma, its management and prevention, origin, and transmission of coronavirus, including the relationship between different CoV infections. Although there is a lack of particular asthma management so far, rectifying the consequences can only be done by taking supportive treatment.

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EXPERIMENTAL

Origin and Transmission

In the 1960s, the two variants of this infectious disease caught sight, named coronaviruses 229E and OC43.[11] Up to the discovery of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002[12], it was disregarded due to its minor severity. The two new coronaviruses, NL63 and HKU1, were identified in 2004 and 2005[13], respectively, as a result of the SARS epidemic. World Health Organization (WHO) had already documented some of the worldwide occurrences of respiratory syndrome. One, known as the Middle East respiratory syndrome coronavirus (MERS-CoV)[14], was discovered in June 2012 in Saudi Arabia and propagated across infecting almost 27 countries till 2018.[15] It is believed that this China epicenter virus has a resemblance with SARS-CoV, due to which it has been named SARS-CoV-2 or COVID-19. In the wake of the identification of the origin of the epidemic virus, researchers went through divergent paths in directive to restrict the spread of the syndrome to humans. There are findings comprehending the role of bats[16] and dromedary camel[17] in spreading infectious diseases. The origin, virus, symptoms, and recommended treatments for MERS-CoV, SARS-CoV, and COVID-19 are discussed in Table-1. Numerous studies indicated that approx. 50% of individuals infected have spread the virus to everyone they come in touch with from the initial start of COVID-19 epidemic. Human transmission, delayed diagnosis, ignored the behavior of doctors as well as patients, intercontinental travel[39], and confined spaces such as hospitals, airports, marketplaces, hotels, and waiting areas[40-48] played an essential role in the outbreak of SARS-CoV-2. It is shocking to recognize that despite having less rate of human transmission than MERS-CoV, the spreading rate of COVID-19 was strikingly higher. The comparative study of symptoms in the percentage of patients affected by different coronavirus epidemics is depicted in Fig.-1. However, the origin and transmission course of SARS-CoV-2 remained evasive.

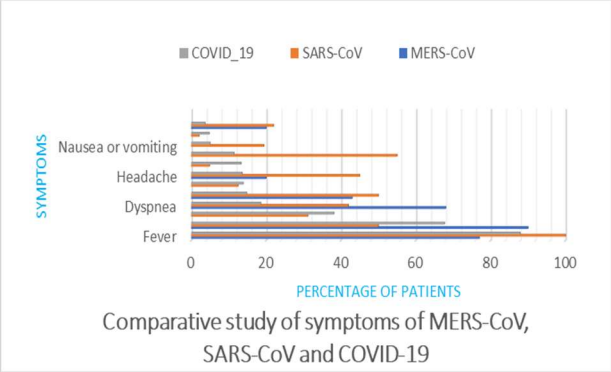

Fig.-1: Comparative Study of MERS-CoV, SARS-CoV, and COVID-19 Patients

Table-1: Comparison of Origin, Virus Type, Symptoms, and Treatment of MERS-CoV, SARS-CoV, and COVID-19

	MERS-CoV	SARS-CoV	Covid-19
Source	Dromedary camels (one-humped camels)	Bat[18]	Bat[19-21]
Virus	β coronavirus	An enveloped, positive-stranded RNA virus with ~30,000 nucleotides[22]	β-COVs, enveloped with subgenus Sarbecovirus, possessing single-stranded positive sense RNA[23, 24]
Symptom	Fever, cough, dyspnea. Sputum production, digestive system signs, odynophagia, myalgia, hemoptysis, and headache have all been documented as subsequent symptoms.	Fever, non-productive cough, fatigue, dyspnea, myalgia, sore throat, headache, expectoration, chills, nausea or vomiting, nasal congestion, diarrhea	Fever, pneumonia, non-productive cough, fatigue, dyspnea, myalgia, sore throat, headache, expectoration, nausea chills, vomiting, diarrhea, nasal congestion, tonsil swelling, conjunctival congestion, hemoptysis, enlargement of lymph nodes, rash

Treatment	Immunotherapy with specification MERS-CoV antibodies[25-27], molecules with antiviral activity such as interferons[28], ribavirin[29], protease inhibitor[30], chloroquine, nitrazoxamide[31], Mycophenolate mofetil[32,33], Alisporivir[34], Silvestrol[35], Extracorporeal membrane oxygenation[36] and symptomatic treatment	Ribavirin, lopinavir/ ritonavir (LPV/r) combination, antiviral therapy[37,38]	No specific therapies. The treatments related to SARS-CoV and MERS-Cov have been recommended.

RESULTS AND DISCUSSION

Pathophysiology of Virus-Induced Asthma

Small extracellular proteins and cytokines serve a crucial part in the synchronization and perseverance of infection in asthma. The antigen in asthma patients, upon recognition and activation by antigen-presenting cells, Interleukin-4 promotes the naive T-cells to distinguish into T helper type 2 (Th2) cells. These cells, further on stimulation, release IgE antibodies having high-affinity receptors at mast cells. Interleukin-9 synergistically promotes the proliferation and differentiation of mast cells. This antigen attack mediates histamine, prostaglandins, and leukotrienes release from the mast cell contributing towards bronchospasm. Moreover, this attack enhances the availability of inflammatory cells, particularly eosinophils, also mediated by IL-5 and IL-9. The generation of mucus and chemokines is gradually increased by epithelial cells.[49-51] A notable rise in abnormal respiratory issues, leukocyte number, and enhanced pro-inflammatory cytokines level in plasma were found in COVID-19-infected patients.[52] Some studies suggest an exceptional rise in the level of chemokines and cytokines and the blood of infected persons, including Interleukin1-β (IL1-β), Interleukin1RA (IL1RA), Interleukin7 (IL7), Interleukin8 (IL8), Interleukin9 (IL9), Interleukin10 (IL10), Interleukin2 (IL2), Macrophage inflammatory proteins (MIP1α), Monocyte chemoattractant protein (MCP1), Granulocyte-macrophage colony-stimulating factor (GMCSF), Vascular endothelial progression or growth factor (VEGFA), Platelet-derived growth factor (PDGFB), Granulocyte-colony stimulating factor (GCSF), Interferon-gamma (IFNγ), Interferon-gamma-inducible protein-10 (IP10), Macrophage inflammatory protein-1β (MIP1β), Tumor necrosis factor alpha (TNFα) and Fibroblast growth factor (FGF2).[53] The increment in the number of cytokines and chemokines advocates that this coronavirus can directly or indirectly influence the smooth muscle contractility reasoned to promote disease severity, but this still remains hidden. The predictable virus-induced asthma pathophysiology is depicted in Fig.-2.

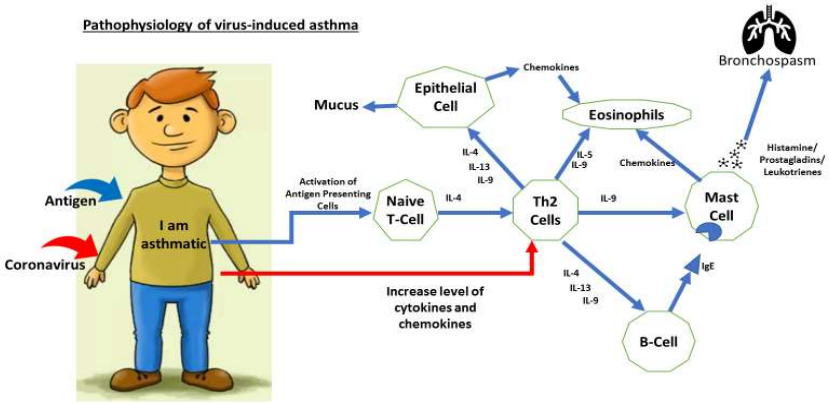

Fig.-2: Virus-Induced Asthma Pathophysiology; Blue Lines Show the Pathophysiology of Asthma and the Red Line Suggests the Predicted Pathway for Virus-Induced Asthma.

Risk Factors for Asthmatics

The exacerbation in asthma executes an essential role in the deterioration of quality of life as well as lung functions. Thus, understanding risk factors that increase the chance of hospitalization and visits to the emergency room can ameliorate management in the treatment of asthma. Notably, asthma exacerbations are associated with chronic sinusitis[54], uncontrolled eosinophilic inflammation[55], sensitivity to

aeroallergens such as animal dander, house dust mites [56-58], drugs [59], extremes in weather or temperatures[60], exercise, respiratory infections[61], cigarette smoke exposure, and diesel exhaust fumes[62], gastroesophageal reflux disease[63], high body mass index, and many unknown factors. There is a probability that a viral epidemic could intensify the airflow obstruction, hyper-responsiveness, and inflammation, declining medical conditions of asthma patients. One of the biggest problems brought on by the global pandemic is that there are no clear clinical signs that can be used to characterize an asthmatic patient. This obstruction could precede the medical confusion in distinguishing between asthma and coronavirus patients, which could only be confirmed post-checkups. Therefore**,** it is anticipated that some individuals may encounter asthma exacerbations during this pandemic.

Risk Management for Asthmatics

Due to the overburden on the medical facility throughout the entire globe, there may be chances of occurrence of deteriorated asthma management. In cases where patients with asthma are suspected of having COVID-19, it is recommended to conduct an interview using a standardized questionnaire. This questionnaire should aim to gather information regarding the patient's symptom history, places they visited while experiencing symptoms, and individuals they came into contact with during that time. The patient history will simulate a key role in this situation as healthcare facilities can review records and design the framework for the exposure risk consequently. The frameworks in the case of asthmatic patients can be implemented as per the documentation done at the time of the former two epidemics. When managing a patient with a history of asthma or chronic obstructive pulmonary disease (COPD) who is suspected or confirmed to have COVID-19, the approach should involve symptomatic treatment and respiratory support as needed. Earlier studies have reported some benefits of melatonin in easing acute respiratory stress caused by viruses, bacteria, radiation, etc.[64-67], a combination of ribavirin and interferon therapy,[68] and recommendations for abiding by the prescribed medication. One of the preferred treatments involves the utilization of dendrimers, which bind to the virus and hinder its replication process, thereby inhibiting viral replication.[69,70] Many pathogens, including hepatitis C, simian immunodeficiency virus, Ebola, HIV, and CMV, infect hosts by binding to dendritic cells' ICAM-3-grabbing non-integrin (DC-SIGN) receptors.[71-80] Some pre-clinical data suggests the preferred use of a PDE4 inhibitor like Roflumilast in case of uncontrolled virus-induced asthma exacerbations.[81] SARS-CoV-2 can survive in aerosols for up to three hours and on surfaces of stainless steel and plastic for up to three days, according to some investigations. It is highly recommended that patients with asthma history take all preventive measures. This includes consuming a diet rich in vegetables and fruits after thoroughly washing them, in addition to following the below mentioned recommendations. It is essential for individuals with asthma to regularly take their prescribed medications as directed by their healthcare provider. Maintaining a supply of at least 30 days' worth of medication is also advised to ensure an uninterrupted treatment regimen.

- Frequently disinfect the surfaces like sinks, doorknobs, countertops, desks, phones, keyboards, handles, toilets, light switches, faucets, tables, etc**.**
- It is crucial to practice proper hand hygiene by washing hands with soap and water or using an alcohol-based solution.
- Refrain from exposure to asthma triggers, persons who have respiratory symptoms, and disinfectants.
- Stay at home during a COVID-19 outbreak.
- Avoid sharing personal items**.**

Effects of COVID-19 Therapy Medicines and Vaccinations on Asthma Patients

There is a persistent argument over the safe use of several vaccines or drugs used for the cure of COVID-19 in asthmatic patients. Promising results of remdesivir against SARS-CoV and MERS-CoV promote its extensive use to treat COVID-19 patients.[82,83,84] Clinical trials showed a shorter recovery period for hospitalized patients in comparison to the placebo group.[84] It is interesting to note that remdesivir is thought to have no effect on asthma because of its mode of action, although there are disagreements over clinical research that support this assertion.[85] Anti-inflammatory medication azithromycin has undergone considerable testing to determine its effectiveness against COVID-19. Owing to its immunomodulatory efficacy, it is regarded as reliable for the treatment of asthma exacerbations without any remarkable threat to asthmatic patients receiving treatment for COVID-19. Further, it has been found that its use for COVID-

19 patients significantly lowers the mortality and severity of SARS-CoV-2 infection.[86,87] Budesonide inhalation is widely regarded as a safe, easily accessible, and cost-effective corticosteroid that is commonly used worldwide in inhalers for the treatment of COPD and asthma. In a multicenter, multi-arm, open-label, adaptive platform randomized controlled trial it has been found that in persons with COVID-19 who had risk indicators for unfavorable outcomes, inhaled budesonide improved recovery time by a median of 3 days.[88] Patients with severe asthma did not have any notable side effects when using the drugs benralizumab, dupilumab, and omalizumab during COVID-19.[89] It has been reported that in a patient with high liver enzyme levels, mepolizumab medication had no negative side effects.[90] The potential for increasing asthma symptoms while receiving COVID-19 vaccines is still being debated, however, as of right now, there is no data to back up such beliefs.[91] The degrees of allergic responses to COVID-19 vaccines are enormously few, with no indication of asthmatics being more susceptible to such hypersensitive reactions. There have been claims that less than 20% of patients who have severe asthma and are on biological treatment reported side effects after vaccination with Pfizer, most of which were categorized as quite common adverse effects. However, according to a weekly report from the CDC, 2.5% of 1 million doses of Modern vaccination participants reported experiencing anaphylaxis. However, 11.1 cases of anaphylaxis per million doses were reported for the Pfizer vaccine.[92] Asthma patients are now encouraged to get the entire course of COVID-19 vaccinations if there are no serious side effects observed after receiving the first dose. The American College of Allergy, Asthma, and Immunology (ACAAI) states that even asthmatics who have been administered ICS or OCS must have the vaccination if there are no serious adverse effects.

Current Scenario

The ongoing scenario has not only overburdened the healthcare system but also created chaos in contacting people worldwide. At present, isolation of suspicious cases and rapid detection are the only ways to prevent local outbreaks. However, the rapid detection of the infected person is a challenging job. Here the saviors would be the experienced, renowned health community who have been working day and night for the betterment of society. So far, no particular strategy has been recommended neither for COVID-19 nor for asthma management, patients are at stake with supportive treatments. While research on antiviral vaccines is still ongoing, significant progress has been made in this field. However, there is still much work to be done in developing effective antiviral vaccines. Infection control and public health services in general, as well as both in particular, are gravely threatened by these novel pathogens. In-depth education and multifaceted treatment can enhance disease outcomes. Therefore, an accurate understanding of their transmission, reservoir, presenting symptoms, tactics for their inspection, optimum management, as well as preventative actions is needed.

CONCLUSION

The global outbreak of coronavirus has led to its classification as a pandemic, primarily due to the unpredictable nature of its spread and the uncertainty regarding its potential disappearance. This ongoing risk to the community at large necessitates continued vigilance and preventive measures. The main focal points of this outbreak globally involve the rising number of transcontinental trips and mass tourism, which has raised the issue of managing individuals suspected of infection and the lack of effective therapeutic options available to date. The increment in the number of cytokines and chemokines suggests that this coronavirus can directly or indirectly affect the smooth muscle contractility reasoned to promote asthma severity, but this still remains hidden. There are reports of asthma exacerbations as a consequence of the former epidemic versions of coronavirus. However, less than 1% of asthma patients have been hit by the SARS-CoV-2 virus to date, making it infeasible to predict the probability of asthma patients getting infected. Currently, it is crucial for asthma patients to prioritize effective control measures to avoid any potential complications. Both physicians and health officials emphasize the importance of close surveillance and thorough analysis to ensure proper management and prevention of adverse outcomes.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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