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Management of asthma and allergic diseases during the coronavirus disease 2019 pandemic in India

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Abstract

Coronavirus disease 2019 (COVID 19) is caused by the novel coronavirus, which has affected 184 countries and the WHO has declared it a pandemic on March 2020. Allergic diseases such as allergic rhinitis and asthma are exaggerated by viral infections. Symptoms of allergic diseases overlap with COVID 19. Current recommendations include following social distancing and frequent hand washing. Confusion exists regarding the use of corticosteroids, biologicals, and immunotherapy for the treatment of allergic diseases during COVID 19 season. Due to the use of Personal Protective Equipments, reports of contact dermatitis are emerging among health-care workers. Remote consultation, like telemedicine, is a valuable tool in this pandemic. This article aims to provide guidance on the management of allergic diseases taking into consideration existing evidence and guidelines from international organizations and the feasibility of implementation in India.

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Full Text

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) is caused by the novel coronavirus disease-2019 (COVID-19). First reported from the Hubei province of China, it has now emerged as a global pandemic affecting nearly 184 countries. This epidemiological situation is constantly changing and has had a major impact on health-care systems worldwide. It is estimated that available health-care resources might not be sufficient to manage patients with COVID-19. Thus, the strategy of social distancing to “flatten the curve” and reduce the health-care burden is propagated worldwide.

At the time of writing this article, the number of new cases had crossed the 3,267,184 mark worldwide, and India had 40,263 total cases.[1] There is an anticipated increase in the number of cases over the ensuing months. Limited data exist regarding Covid-19 and allergic diseases. This presents a unique challenge to the Allergist/Immunologist, Pulmonologist, Pediatricians, and Otorhinolaryngologists in the diagnosis and management of Covid-19 in patients with allergic diseases due to the overlap in symptoms of common chronic allergic conditions.

Symptomatology

SARS-CoV2 infection presents with varied symptomatology. However, the majority of the symptoms involve the airways and respiratory system. Thus, it is anticipated that the majority of the symptoms may be missed on routine clinical practice as they overlap with respiratory allergies. A brief description and differentiation between symptoms of COVID-19, Flu, common cold, and allergic rhinitis (AR) are given in [Table 1]. The most common early symptoms include fever, cough, and shortness of breath. Rare manifestations such as diarrhea and anosmia are also being increasingly identified.[Table 1]

Susceptibility of Allergic Diseases to Coronavirus Disease 2019

Viral infections are the most common cause of exacerbations of allergic diseases, including asthma.[2],[3] Most commonly, these are secondary to rhinovirus (60%–70%) and paramyxoviruses.[4] This is considered to be due to reduced local epithelial immune response, such as decreased cytokines like interferon- β . [5] Raised T-Helper 2 (TH2) to T-Helper 1 (TH1) ratio has also been found to be associated with higher susceptibility to viral infections. Th1 response is necessary for anti-viral mediation. Eosinophilic inflammation in response to upper respiratory tract infections and raised neutrophilic inflammation in the lower respiratory tract is also associated with increased bronchial hyper-responsiveness and exacerbations.[6],[7] Certain milder strains of coronavirus (Non-COVID 19) have been demonstrated to be present in airways of asthmatic patients during exacerbations.[8]

Early reports from South Korea and China suggest similar susceptibilities among the asthmatic and general population.[9],[10] One report from China found that asthma and respiratory allergies were not significant risk factors for severe COVID 19 disease.[11] Analysis of SARS-CoV2 revealed that it binds with Angiotensin-I Converting Enzyme 2 (ACE2) receptor.[12] ACE2 receptor is expressed in many organs, especially the Type II Alveolar epithelial cells. In vitro studies showed increased susceptibility for cells expressing higher ACE2 receptors, and further studies revealed that ACE2 receptors were upregulated in association with smoking, diabetes, and hypertension—conditions with higher susceptibility to severe COVID 19 disease. [13],[14] One recent study from the USA assessed ACE2 receptor in nasal epithelial cells of atopic children and allergic adults. They found that in children with moderate to severe allergic sensitization, ACE2 receptors were downregulated when compared to mildly sensitized children. They also found that there was an inverse relationship between type 2 inflammatory markers and levels of ACE2. In adults with known respiratory allergies, it was found that the respiratory epithelial ACE2 expression was reduced upon allergen challenge.[15] This finding could explain the lower incidence of severe COVID 19 disease among patients with respiratory allergies and asthma. However, Indian data are currently lacking, and findings thus far cannot be generalized. Data from pediatric age group are also lacking. Since other variants of coronaviruses have been associated with asthma exacerbations, susceptibility of patients with

asthma to COVID 19 cannot be ruled out at this moment.

Although a different local immune response has been found in patients with AR to rhino and paramyxoviruses, susceptibility or resistance to COVID-19 in comparison to the general population cannot be determined at the moment.[16] However, poorly controlled AR or those not on medications increases the probability of infection. Symptoms such as rhinorrhea, sneezing, and itching of eyes and nose could lead to further dissemination of nasal secretions, which can enhance the spread of infection. Such symptoms also naturally force a patient to come in contact with these surfaces and increases contamination.

There is also no data as of yet regarding the susceptibility of other allergic diseases such as allergic skin diseases, food, and drug allergies, anaphylaxis, and insect sting allergies to COVID 19.

General Practice Essentials

Since Covid-19 is highly infectious, care for patients and health-care staff, including the doctor themselves, is of paramount importance. Knowledge regarding local referral centers for diagnosis and management of COVID 19 cases is advisable. General infection control principles to restrict infection exposure and spread should be followed. Measures such as physical distancing of up to 1 m when in public, limited social movements and contacts, regular handwashing with soap, cough and sneeze etiquette and their importance should be explained to health-care staff and patients. It is also advisable to display visual alerts such as posters and sign explaining about hand washing and hygiene in strategic places within the clinic. Health-care staff should be designated clear roles and trained adequately before managing patients. Triaging and management of suspected COVID 19 patients should be done separately. The availability of adequate Personal Protective Equipment (PPE) should be ensured for both staff and doctors. Follow local guidelines regarding the use of PPE and its disposal. Since most allergic disorders have a chronic course, it is advisable to reduce patient footfall and encourage electronic or teleconsultations, especially for those patients with stable disease. In the case of direct visits, patient seating can be adjusted to maintain physical distancing. Procedures routinely used for diagnosis of allergic diseases will need to be postponed for the time being due to the risk of aerosol generation and increased patient and health-care staff risk. [Table 2] shows a list of procedures that need to be avoided during COVID 19 pandemic.{Table 2}

Management of Allergic Asthma

Bronchial asthma is a complex inflammatory disease of the lower airways. The number of patients with asthma is estimated to be between 1.7 and 3.0 crores in India.[17] A variety of influences such as genetic predisposition, comorbidities, reduced adherence to medications, etc. are responsible for asthma control. The first step in the management of asthma, in general, is the identification and correction of these potentially modifiable risk factors.[18] Prevention of exacerbations is one of the major goals of asthma therapy, and inhaled corticosteroid (ICS) has been the most important controller medication in the management of bronchial asthma. It is the first line of choice for controller medicine in almost all varieties and severities of asthma. Achieving good asthma control using ICS has been found to be associated with reduced susceptibility to exacerbations due to rhinovirus infections.[19] Early in vitro studies suggest reduced cytopathic effect of SARS-CoV2 on respiratory epithelial cells with ciclesonide.[20],[21] ICS use is also postulated to reduce lung inflammation and lung damage secondary to COVID 19 infection.[21] [Figure 1] depicts the possible role of ICS in COVID 19 and chronic lung diseases.[22] Loss of asthma control is anticipated to increase emergency hospital visits and subsequent high exposure risk for the patient. Asthma symptoms such as cough could worsen during medication withdrawal and in asymptomatic COVID-19-infected patients can still lead to the dispersion of infection. ICS withdrawal is likely to be associated with more harm, and it is thus recommended to continue using regular controller medications with or without LABA for asthma control. Daily ICS has been found to be superior to the use of Leukotriene Receptor Antagonists (LTRA) as controller medication in pediatric age group as well.[23] Thus, there is enough evidence to continue ICS use to maintain adequate asthma control. Metered-dose inhalers with spacer (single patient use only) or dry powder inhaler are preferred routes for ICS administration as nebulizer use increases the risk of aerosolization. Using a written action plan for the management of symptoms and exacerbations should be encouraged. In the case of stable patients, prefer teleconsultation.{Figure 1}

Systemic corticosteroids are routinely used in the management of asthma flare-ups or exacerbations. There are contradicting suggestions as to the use of systemic corticosteroids in

patients with asthma. World Health Organization and the Center for Disease Control and prevention, USA suggest not to use systemic corticosteroids in the setting of COVID 19 pandemic due to the risk of worsening lymphopenia and exaggerated inflammation.[24],[25] However, Global Initiative for Asthma and National Institute for Health and Care Excellence suggests using a short course of systemic corticosteroids for exacerbation management in patients with asthma[26] or severe asthma.[27] The use of corticosteroids in previous coronaviruses infections such as Middle Eastern Respiratory Syndrome, and SARS revealed that there was an increased duration of viral shedding and worse clinical outcome. There is also early evidence suggesting the response of COVID 19 to systemically administered corticosteroids from China.[28],[29] Furthermore, about 4% of patients with severe asthma[30] are on chronic systemic corticosteroid therapy. Withdrawing corticosteroids in this subset of patients would not only lead to loss of asthma control but also potentially exposes the risk of adrenal failure (secondary to chronic adrenal suppression). Thus, care must be exercised in deciding systemic corticosteroid use in patients with asthma. It is advisable to use systemic corticosteroids in asthma exacerbations in patients without COVID 19. However, its use in COVID 19 positive asthma exacerbations is to be decided by the treating physician. Emphasis should be placed on advising such vulnerable patients to maintain physical distancing and strictly follow government recommendations regarding shielding and isolation. Currently, there is no data suggesting the relevant role of other controller medications such as LTRAs and beta-adrenergic agonists (Short- and Long-acting) in COVID 19 disease process, and they can be used regularly as before.

Anti-IgE and anti-interleukin (IL)-5 and other biologicals are recommended in the management of severe asthma according to many guidelines.[26],[31] They help in achieving and maintaining symptom control in patients with severe bronchial asthma. Currently, there is no evidence that ongoing treatment with biologics could increase susceptibility to SARS-CoV2. Thus, they can be continued according to local guidelines and also encourage patient self-administration where possible such as in Europe.[32],[33]

Management of Allergic Rhinitis

Allergic rhinitis (AR) is the most common allergic disorder among the Indian population. Seasonal and perennial AR symptoms equally lead to a poorer quality of life and reduced work or school performance. Sneezing and Rhinorrhea are predominant symptoms, while nasal congestion, headaches, and conjunctival itch can also occur in a subset of patients. Symptoms of AR can strongly mimic that of seasonal flu, rhino-viral infections, or even COVID 19 [Table 1] gives differentiating features of these conditions] where sneezing is a rare symptom. Anosmia with nasal congestion or nose block is also a common scenario in AR. Anosmia has also been reported as an early symptom of COVID 19.[34] Due to the nature of these symptoms, contact with the patient's own hands are common with the eyes and nose and can lead to infection and also acts as a fomite for transmission. It is recommended that direct patient visits for evaluation and management of AR can generally be postponed or avoided, and where direct visits are necessary ENT evaluation should be avoided.[35] Using remote communication methods such as teleconsultations can be preferred for their management. Apart from educating about regular hand washing and sneeze etiquette, these patients should be treated as per established guidelines. Avoidance measures are still the first-line management in AR. Pharmacotherapy for mild intermittent AR can be continued with second generation non-sedating oral antihistamines. An added benefit with them is the reduction in sneezing and eventual droplet transmission. Enough evidence exists for the role of intranasal steroids (INS) in the management of AR and is recommended for treatment in persistent AR and patients with nasal congestion.[36] INS use leads to improvement in nasal patency and reduces the loss of smell. However, anosmia as a solitary presentation has been described in COVID 19. Considering this, in the absence of nasal congestion, it is not recommended to use INS for anosmia. [37] Based on data extrapolated from asthma recommendations, an EAACI-ARIA statement recommends continuing to use INS in AR with or without COVID 19.[38],[39] For severe persistent symptoms, a combination of INS with intranasal antihistamine is recommended. In vitro testing (serum specific IgE) is preferred over skin prick testing (SPT and IDT) for allergen evaluation in such patients due to disadvantages of withholding antihistamines (skin testing) and potential worsening of symptoms along with exposure risk while visiting clinic/hospital.

Management of Skin Allergies

At the moment, there is no evidence for the link between allergic skin disorders and increased susceptibility to SARS-CoV2. Acute Urticaria has been commonly associated with influenza, enterovirus, RSV, EBV, and CMV. CMV has also been reported to be associated with chronic urticaria.[40] Early reports from China suggest <2% of patients diagnosed with Covid 19 presented with urticaria as their first manifestation.[41] Another study from Lombardy, the epicenter of COVID 19 pandemic in Italy, found that nearly 20.4% of patients with COVID 19 had some form of cutaneous manifestations. Amongst them, nearly 3% presented with Urticaria.[42] A case report of a young female presenting with urticarial rashes as the first manifestation of COVID 19 was also recently published.[43] New or first visit mild and moderate cases of angioedema can be managed with remote consultations. Severe cases may need admission and

evaluation. For a new patient with urticaria, it is advised to begin treatment with double dose of 2nd generation nonsedating antihistamines. Second-line treatment is usually with Anti-IgE according to many international guidelines. Treatment with biologicals has not been shown to increase susceptibility to viral infections. However, to reduce frequent visits for injection administration, it is advised not to begin Omalizumab for second-line management of chronic spontaneous urticaria if not already on it.[44] If the patient is already on Omalizumab, self-administration of injection after completion of the first 2 doses by a physician is suggested. This is already approved and in practice across several centers in Europe.[33] If patients are on chronic systemic corticosteroid use, then it may be continued or gradually tapered with advice on self-isolation and practicing strict hand hygiene.

Atopic dermatitis (AD) is a challenging scenario. While most patients with mild disease will benefit from topical corticosteroids and emollients, it is the severe variant that needs careful attention. Moderate and severe AD who are on treatment with immune-modulating or immunosuppressive medications (topical and systemic) develop worsening skin lesions and infections upon withdrawal. On the other hand, immunosuppressive medications increase risk of disseminated viral skin disease. However, such relationship between SARS-CoV2 infection and AD has not been reported.[41] Thus, a careful weigh-in of all possible options is needed. The European Task Force for AD recommends continuing immune-suppressive medications and advice such patients to follow regular hand hygiene and measures for infection prevention as per local guidelines.[45] General measures like using nonirritant soap substitutes and the application of moisturizers afterward are recommended. If immunosuppressive medications have to be paused, treatment must be adequately supplemented with ample topical therapy. Targeted therapy like Dupilumab (Anti IL-4) has not been reported to increase susceptibility to viral infections; thus, it may be continued in patients already on it and might even be preferred over conventional treatments like ciclosporin.[45]

Reports of contact dermatitis have emerged among health care workers with prolonged contact with PPE and excessive hand sanitizer use.[46] Symptoms include burning, itching, and stinging sensation. Wearing uncomfortable PPE for a prolonged period leads to hyperhydration state and worsening AD in predisposed individuals. Occlusion caused by prolonged glove use also results in contact dermatitis. The commonest site of contact dermatitis in this scenario is the nasal bridge due to goggle use. Contact dermatitis and pressure urticaria have also been commonly reported secondary to prolonged mask use. It is recommended to apply moisturizers and emollients over sensitive regions after hand washing before donning PPE.

Management of other allergic diseases (food allergy, drug allergy, anaphylaxis, gastrointestinal allergies)

Most patients with anaphylaxis, Eosinophilic Esophagitis (EoE), and anaphylaxis are in generally better health state than asthma, AR or eczema. Thus, most of the patients (with rare exceptions) may be evaluated over remote consultations (telephonic or video) until the pandemic subsides. Challenge tests are an important tool in the management of food and drug allergies. However, they need in-person visits and may even require admission. Thus, to reduce exposure risk, it is generally recommended to avoid challenges except in the following scenarios:[44]

Milk/soy/formula feed introduction in an infant with suspected or proven food allergies, Food Protein induced Enterocolitis Syndrome (FPIES) or EoE Essential grain or nutrient which has been withheld due to misdiagnosis with an urgent need to reintroduce in diet Patient labeled with drug allergy with the urgent need for— desensitization or de-labeling.

The following food challenges are not considered as an emergency and deferred till the pandemic situation improves:

Baked milk or egg challenge Nonessential nutrient challenge Reintroduction of avoided food in EoE Check overgrowth of nonIgE allergy in FPIE Evaluation of food allergies in AD.

For patients with diagnosed anaphylaxis, pre-filled adrenaline syringes can be provided in advance to avoid frequent refilling/buying. For patients with new-onset anaphylaxis, admission and evaluation are warranted.

Role of allergen immunotherapy

Allergen immunotherapy (AIT) is a disease-modifying treatment available for IgE mediated respiratory allergies and venom hypersensitivity. Specific immunotherapy can be given either as subcutaneous injections (Subcutaneous Immunotherapy [SCIT]) or as Sublingual drops/tablet (Sublingual Immunotherapy [SLIT]). SLIT is currently not approved in India (DCGI). SCIT is given in 2 phases – a gradual up-dosing (the “build-up” phase) followed by regular “maintenance phase”. In the build-up phase subcutaneous injections are administered weekly once or as weekly twice doses. In maintenance phase, injections are administered once in 2–4 weeks. Every injection has to be administered in the healthcare facility with back up resuscitation equipment. Generally, there is a wait period of 30 min following SCIT administration. During the period of Covid 19 pandemic, it is advisable to avoid beginning new SCIT for treatment of

allergic diseases since there is a need for frequent hospital visits and administration. Recommendations from various guidelines is summarised in [Table 3].[38],[44]{Table 3}

Challenges in Indian scenario

Around 25% Indians suffer from some form of allergic disorder.[47] AR (20%–30%) is the most common allergic disorder in India.[48] Symptoms of AR is usually overlooked by the patients and untreated in most of the cases as reported in study by Sinha et al.[49] who noticed that in the absence of asthma, only 40% patients with AR took medical treatment. Since the symptoms overlap with Covid 19, there is resultant exaggerated fear and panic among patients or in the other end of the spectrum, patients may neglect possible Covid 19 disease as AR and continue to be active spreaders.

Asthma prevalence is close to 2%–3.5% in Indian population.[50] Although this is lesser than worldwide prevalence, the absolute number of patients due to the large Indian population is a large healthcare burden. Most patients are on treatment, however a study found that 60% of asthma patients experienced at least one exacerbation in the previous year and of them 49% patients experienced 3 or more exacerbations.[51] The same study also revealed that 91% asthmatics felt their disease was controlled however, 100% of these patients failed to satisfy the guideline based control status. Studies have shown predisposition to viral exacerbations in patients with loss of asthma control.[2] This puts asthmatics in a tricky situation during Covid 19 pandemic especially during the oncoming winter months when asthma exacerbation frequency is higher. Only a small percentage of patients have been found to use ICS as controller medicines[51] and most patients in India are comfortable with relievers due to “steroid stigma”.

Tools for the diagnosis and management of allergic disorders are not universally available. Investigations such as peak flow meter, spirometry, and SPT are easy to perform and provide immediate results and appropriate in Indian scenario. However, as a result of the ongoing pandemic, these cannot be used as part of general safety measures unless absolutely necessary. Despite international recommendations to use serum specific IgE, cost, and availability is a major limiting problem.

Telemedicine is a new tool recently legalized and approved for use in India by the Ministry of Health and Family Welfare.[52] Both doctors and patients are relatively new to using this new form of technology for disease management. Telemedicine has obvious advantages: convenient and accessible patient care, reduced patient contact, ease of referral etc. However, there are caveats such as lack of physical examination, universal availability, technical training (both doctor and patient)-all of which are of major concern in the Indian scenario. Excepting emergencies, telemedicine could be used for the time being to manage chronic conditions, most of which include stable allergic disorders. Due to the obvious benefits particular to the current pandemic scenario, its utilization is anticipated to improve with time. The feasibility of telemedicine and taking prior appointment is a challenge as most part of daily practice is direct “walk-in” visits.

Finally, allergy as a specialty is not yet recognized in India. There are many short course training programs, but the majority of allergy practice is done by specific organ specialists such as otorhinolaryngologist, pulmonologist, pediatrician and general practitioner. Lack of training or knowledge regarding allergy as a multi-system disorder and nonadherence to established national and international guidelines can lead to incomplete management and persistent symptoms. Hence, there is a need for introducing allergy early into the medical curriculum.

Summary

COVID 19 disease cases are on the rise worldwide and are expected to affect a significant part of the world population. Allergic diseases have been on a rise in the last few decades and a large number of Indians suffer from allergies. Early reports suggest patients with allergic diseases are less likely to develop severe COVID 19 disease. Most Indians suffer from uncontrolled allergic diseases, which could increase susceptibility to SARS-CoV2. Guidelines are currently available from international organizations regarding the management of allergies during COVID 19 pandemic. Adequate disease control for asthma using ICS is recommended. Systemic corticosteroids can be used with caution in early exacerbations; however, COVID 19 symptoms should be closely monitored. Biologicals can be used in severe disease states and self-administration can be considered to reduce patient visits. In the current scenario, it not recommended to begin AIT with Aeroallergens. If the patient is already on AIT, it can be continued with increased dose intervals to 6–8 weeks in the maintenance phase. Emphasis should be placed on using remote consultation technologies like telemedicine to reduce unwarranted patient visits. Adequate patient and parent education regarding cough etiquette, physical distancing, and hand hygiene while following government regulations should be prioritized.

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Conflicts of interest

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