

Review



Management of Allergic Patients During the COVID-19 Pandemic in Asia

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ABSTRACT

Although a viral infection is a major triggering factor of asthma and allergic diseases, asthma is suggested to be not a predisposing condition for coronavirus disease 2019 (COVID-19) infection. However, patients with severe asthma/allergic disease requiring systemic corticosteroids or immunosuppressive agents may be at higher risk of more severe clinical course of this infectious disease. For allergic patients who have been followed up at an allergy clinic in our region, it is recommended that they (patients with asthma, rhinitis, atopic dermatitis or chronic urticaria) continue to receive maintenance therapy and be in a well-controlled status. Patients who have used biologics (currently available for targeting type 2 inflammation) and allergen immunotherapy should continue the treatment while minimizing hospital and face-to-face visits. It is essential to wear protective equipment for the protection of health care workers as well as patients. We report this consensus to support allergists and clinical immunologists to make optimal decisions under the urgent situation in Asia.

Keywords: Coronavirus; pandemics; Asia; allergy and immunology; asthma; rhinitis; atopic dermatitis; chronic urticaria; management; immunotherapy

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has started from Wuhan in China in late December 2019; the World Health Organization (WHO) named this new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case of person-to-person transmission was confirmed in January 2020, and the first wave of the pandemic has started across the globe, including in Asian countries.¹ The case-fatality rate among infected patients varies in our region: 5.5% in China, 2.2% in Korea, 2.5% in Japan and 0.1% in Singapore, which is lower than in the US and European countries.² Higher mortality rates (8%–15%) were reported in elderly patients and patients with comorbid conditions such as hypertension and metabolic diseases.^{1,3} In addition, an important issue is the spreading of this infection to healthcare workers (HCWs). In China, 3.8% of the cases were found in HCWs (14.8% among

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them were severe or critical) with a mortality of 0.3%; moreover, 63% of the affected HCWs were reported in Wuhan.⁴

The prevalence of allergic diseases, including asthma and allergic rhinitis (AR), is increasing in Asian countries, especially in the elderly,^{5,6} in which viral infections are major triggering factors. Although the initial starting point for COVID-19 appears to have been successful in controlling epidemics to the appropriate initial response in this region, there is constantly the possibility that a new virus subtype outbreak will begin.^{7,8} Therefore, we report our consensus on how to manage allergic patients during this pandemic as well as how to protect HCWs.

To prevent the spread of this viral infection, the specified preventive measures have been applied to the general public and HCWs. The WHO recommended basic protective measures, including frequent hand washing, maintaining a social distance of 2 m and practicing respiratory hygiene for the public.⁹ During the COVID-19 pandemic, hospital authorities in Korea have restricted entrance to the hospital through strict screening of people by checking recent travel history, clinical symptoms and body temperature. Furthermore, all the patients have been asked to wear a disposable facial mask with careful monitoring of symptoms and temperatures during their stay in the hospital. The American Centers for Disease Control and Prevention (CDC) recommended appropriate personal protective equipment for healthcare providers, including gowns, gloves, N95 respirators and goggles.^{1,10}

THE RISK OF COVID-19 IN PATIENTS WITH ASTHMA AND ALLERGIC DISEASES

Although a respiratory viral infection is a major contributing factor to asthma exacerbation as well as a triggering factor, information about the influence of SARS-CoV-2 on asthma and allergic diseases is limited. It was reported that none of the 140 patients who were hospitalized due to confirmed COVID-19 in Wuhan, China had asthma or other allergic diseases such as AR, atopic dermatitis (AD) and food allergy.¹¹ Drug hypersensitivity and urticaria were found in 11.4% and 1.4% of the patients, respectively, in that study; their relationships to COVID-19 remain unclear. Another report from Wuhan observed a markedly lower prevalence of asthma (5 asthmatics among 548 patients with confirmed COVID-19, 0.9%) compared to the prevalence of adult asthma in Wuhan (6.4%).¹² In another recent study of the 1,099 patients with COVID-19 admitted, no asthmatics were found among the study subjects.¹³ Korean data demonstrated that none of the 22 patients who died of COVID-19 were suffering from asthma or other allergic diseases.³ However, the possibility of under-diagnosis or under-reporting exists in those studies. Although it has not been determined whether allergy or asthma may predispose patients to COVID-19, non-pandemic coronavirus infections have aggravated asthma both in adults and children.^{14,16} Thus, the probability of the aggravation of asthma and other allergic diseases by COVID-19 should be considered. Furthermore, as pediatric patients with asthma are at higher risk of respiratory viral infections, most experts advise extreme caution in such cases.¹⁷

Immunosuppressive agents are frequently used to achieve a well-controlled status in patients with asthma or severe allergic diseases. Systemic corticosteroid, one of the most widely used rescue medications in allergic diseases, is known to increase the risk for systemic infections, and so do other immunosuppressive agents such as methotrexate and cyclosporin.¹⁸ Fortunately, the advent of biologic agents, such as anti-immunoglobulin E (IgE), anti-

interleukin (IL)-5 and anti-IL-4 antibodies, has improved treatment outcomes with reduction in medications including systemic corticosteroids. As it is not clear whether biologics may increase the susceptibility to serious infections, further studies are needed to draw conclusions. Taken together, we should consider the possibility of bidirectional influences between COVID-19 and asthma/allergic diseases, which can be influenced by patients' clinical characteristics such as age, comorbid illnesses, and profiles of the medications.

PRACTICE OF ALLERGEN IMMUNOTHERAPY

Allergen-specific immunotherapy (AIT), including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), is widely applied to patients with asthma or AR in Asia.¹⁹⁻²² AIT, especially SCIT, requires long-term regular contacts between HCWs and patients (>3 years). During the COVID-19 pandemic, home isolation strategy is necessary to control this highly contagious disease, and frequent hospital visits may increase the risk of exposure to the virus.

To prevent the risk of infection and to provide safe medical services, the following control measures have been suggested to patients undergoing SCIT in each allergy center.²³ Whenever the patients visit the hospital, they should be asked to take strict screening of COVID-19 at the entrance and exit. Only patients with a normal temperature are allowed to enter the outpatient clinic. They should wear a disposable surgical mask during their stay in the hospital. Any confirmed cases of COVID-19 should stop AIT until this infection completely resolves and the viral test result becomes negative.²³

A good piece of advice is for HCWs, including physicians, nurses and the administrative staff contacting with patients, to wear appropriate personal protective equipment such as N94/95 protective masks and latex gloves in Korea, while additional protective equipment, including waterproof medical caps, anti-fog protective goggles and protective face shields, is required in allergy centers in Beijing.

Injections for SCIT should be modified after case-by-case assessment. At the up-dose phase, discontinuation of SCIT is recommended if regular visits to the allergy center are difficult. Re-initiation can be planned until continuous visits are available. In patients who are at the maintenance phase of SCIT, the injection protocol can be adjusted later, and the next dose can be administered again as recalculated according to the authoritative guidelines. SLIT can be continued without interruption.²³ Online consultation and medicine delivery services are recommended to reduce the need for patients to visit or stay in an allergy center during the COVID-19 pandemic.

PHARMACOLOGIC TREATMENT

Asthma (adult and childhood) and AR

It is well known that common coronaviruses are associated with the worsening of asthma symptoms.^{14,15} Recent reports have suggested that asthma does not increase the risk of COVID-19 infection or related complications.^{3,11,13} However, these data have been obtained from hospitalized patients with COVID-19; therefore, the actual risk has not yet been accurately determined. The WHO recommends avoiding systemic steroid use in patients with COVID-19 (not limited to asthmatic patients), except in some situations such as septic

shock and acute respiratory distress syndrome.^{11,24-26} All asthmatic patients should be treated with inhaled corticosteroids (ICSs) with/without long-acting beta₂-agonists as controllers according to the Global Initiative for Asthma (GINA) guidelines.²⁷ It would be better to use a metered-dose inhaler or dry-powder inhaler rather than a nebulizer in order to prevent the risk of the spread of the virus via the device.²⁸ If patients with mild-to-moderate asthma are well controlled and have sufficient maintenance medications, it would be better to postpone face-to-face visits along with online consultations.²⁹ Considerable efforts should be made to reduce the prescribed dose of systemic corticosteroids in order to avoid an immuno-compromised status in the management of severe asthma. Elderly patients with asthma or comorbid conditions should be more strictly monitored. Additionally, it is recommended that regular Ig replacement treatment be maintained in asthmatic patients with IgG subclass deficiency suffering from frequent asthma exacerbations.³⁰ Such patients should receive IgG replacement treatment during the pandemic, even though they have the risk of exposure to the virus during their visits in order to prevent asthma exacerbation.³¹ Taken together, it is important to maintain each patient in an optimal controlled status, and it is not recommended to step-down controller medications that are maintained.^{29,32} If patients have asthma exacerbations, they should be managed according to the GINA guidelines. When conducting lung function tests to monitor control status, the clinical necessity and potential risk of droplet infection are compared carefully based on the judgment of the clinician. It is recommended to perform spirometry only when its results can draw an immediate treatment decision.³³

No specific documents are available for the management of AR during the COVID-19 pandemic; therefore, stepwise treatment should be performed according to symptom severity. However, given the benefits of controlling AR in patients who also have asthma, AR should also be treated more actively.³⁴ In cases of mild/intermittent AR or seasonal rhinitis, face-to-face consultation should be postponed, and instead non-face-to-face consultation (online consultation) is advisable.

From the data available, it is currently clear that children are far less affected by COVID-19 than adults and that clinical symptoms are usually milder in children than in adults.³⁵ Moreover, according to data from the American CDC, it is found that the prevalence of asthma in children (n = 345) with COVID-19 is about 11.5%, which is lower than that in the general population (20%). However, these data must be interpreted with caution because the total number of children included in the study was relatively small, and there was a considerable amount of missing data.³⁶ Although specific studies on the effect of COVID-19 in asthmatic children have not been published yet, COVID-19 may not be an asthmogenic virus in children. In a review article, it is suggested that pediatric allergists should treat patients with asthma, AR or other allergic conditions according to the usual guidelines. In addition, there is no evidence that currently available asthma and allergy medications, including antihistamines, ICSs and bronchodilators, increase the risk of disease exacerbation by COVID-19. It is also not advisable to stop oral steroids in the management of asthma if the patient is already taking these medications or to avoid oral steroids for the treatment of an acute asthma attack even if it is due to COVID-19.³¹ Although additional studies are needed in patients with pediatric asthma, it seems that COVID-19 is not a risk for asthma exacerbation in healthy or asthmatic children. During the current pandemic, asthmatic children should continue to receive preventive treatment in order to be under good control. There have been no studies on the effect of COVID-19 on AR in children yet. The Allergic Rhinitis and its Impact on Asthma (ARIA)-European Academy of Allergology and Clinical Immunology (EAACI) mentioned that patients with common allergic conditions do not develop additional distinct symptoms or seem to be at increased risk of severe disease when infected with COVID-19.³⁷

Atopic dermatitis

AD is a chronic inflammatory skin disease characterized by recurrent eczematous skin lesions and pruritus. Not only is AD associated with airway diseases such as asthma and AR, but patients with severe AD are also likely to be vulnerable to respiratory infections because of their systemic immunosuppressive treatment.³⁸ However, discontinuation of immunosuppressive agents should not be applied in all AD cases, since it can lead to the aggravation of AD and even to disseminated viral skin diseases such as eczema herpeticum.³⁹ Maintenance of skin hygiene and the use of moisturizers and topical immunosuppressive agents would be preferable options in the treatment of AD. However, systemic immunosuppressant or immune-modulating agents, such as dupilumab, seem unlikely to elevate the risk of COVID-19. A recent Italian study reported that only 2 (0.82%) of 245 AD patients treated with dupilumab developed COVID-19, and they successfully recovered from COVID-19 while maintaining dupilumab therapy.⁴⁰ Taken together, to maintain optimal skincare, topical immunosuppressant and immune-modulating therapies should not be deferred or stopped if needed on the basis of physicians' judgment to prevent flares of AD.

Chronic urticaria (CU) and drug allergy

CU is defined as urticaria that has been present for at least 6 weeks and required long-term maintenance therapy because symptoms can last for years in many cases.⁴¹ In healthy subjects without any underlying diseases, CU symptoms are not usually life-threatening, and visiting healthcare facilities needs to be delayed and rescheduled (a few weeks to a few months) during the COVID-19 pandemic. To avoid this highly contagious disease, it is necessary to reduce unnecessary visits to hospitals and to be isolated at home. In particular, older patients with comorbidities, such as hypertension, diabetes, cardiovascular disease and chronic respiratory disease, are vulnerable to infections and are more cautious in visiting hospitals.^{42,43} However, visiting healthcare facilities would be of some benefit in patients experiencing significant deterioration in the quality of life without regular medication. When patients develop severe symptoms, such as anaphylaxis, angioedema, bronchospasm, dizziness, and hypotension accompanying urticaria, they should visit the emergency department to treat symptoms. Patients are required to follow all the policies for infection control. Physicians should delay the evaluation of the causes of CU and reschedule patient outpatient visits until the pandemic is over.

Drug allergy can be managed according to similar basic principles. Drug allergy should be immediately treated especially in the presence of symptoms, such as generalized urticaria, angioedema, bronchospasm and hypotension. Epinephrine injection is contemplated in cases of suspected anaphylaxis. Diagnostic procedures, such as drug challenge and drug skin tests, are required to be delayed until the pandemic is over. Drug desensitization is actively considered in patients who need immediate administration of hypersensitivity drugs. In principle, desensitization needs to be performed in the hospital according to the infection control procedure.⁴⁴

BIOLOGIC TREATMENT

Regular administration of biologics, such as anti-IL-5, anti-IL-4 and anti-IgE antibodies, has become a common treatment option for severe asthma as well as for uncontrolled cases of CU and AD. It is critical to control disease activity through the prevention of exacerbations.⁴⁵ In addition, there have been no studies showing that biological agents may induce immune

suppression and increase the risk of COVID-19. For these reasons, there is no need to stop or reduce the dosage of biologics scheduled.²⁹ However, most of the biologics require periodic parenteral/subcutaneous administration, for which such patients have to visit an allergy clinic to receive medications according to a treatment protocol. In these patients, it is advisable to provide required protective equipment to both HCWs and patients and to administer the medication with minimal contact.^{9,10}

In allergic children, biologics are mainly used in patients with severe eczema or severe asthma. There have been no studies or guidelines on the usage of biologics in allergic children during the COVID-19 pandemic. A case report suggested that immunosuppressive therapy with biologics might be effective in COVID-19 patients with an overactive immune response, cytokine storm; however, there have been no systematic studies on this.⁴⁶ When children under treatment with biologics are infected with COVID-19 and present with only mild symptoms, the treatment can be continued. However, when either adults or children who develop severe COVID-19 symptoms, the treatment should be delayed until they completely recover.

CONCLUSION

It is still uncertain whether COVID-19 increases the risk of aggravating asthma or allergic diseases. Detailed monitoring and optimal treatment with AIT, ICS and biologics need to be continued in all patients suffering from asthma and allergic diseases. This can be achieved in a safe condition using optimal protective measures. Patients at high risk (older age and comorbid conditions) should be monitored more strictly. We applaud all the allergy/immunology specialists who strive to stay up for optimal health protection by focusing on patient management during the COVID-19 pandemic.

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