

Coronavirus disease 2019, allergic diseases, and allergen immunotherapy: Possible favorable mechanisms of interaction

Désirée E. Larenas-Linnemann, M.D.,¹ José A. Ortega-Martell, M.D.,² María V. Blandón-Vijil, M.D.,³ Noel Rodríguez-Pérez, M.D.,⁴ Jorge A. Luna-Pech, M.D., Ph.D.,⁵ Alan Estrada-Cardona, M.D.,⁶ Alfredo Arias-Cruz, M.D.,⁷ Blanca E. Del Rio-Navarro, M.D.,⁸ Elsy M. Navarrete Rodríguez, M.D., Ph.D.,⁸ Cesar F. Pozo-Beltrán, M.D.,⁹ Ernesto Onuma Takane, M.D.,¹ María I. Rojo-Gutiérrez, M.D.,¹⁰ Francisco J. Espinosa-Rosales, M.D.,¹¹ and Eric A. Martínez-Infante, M.D.¹²

ABSTRACT

Background: Both, allergen immunotherapy (AIT) and SARS-CoV-2 infection cause a set of immunologic changes that respectively vary during the course of the treatment or the disease.

Objective: To review immune changes brought along by each of these entities and how they might interrelate.

Methods: We start presenting a brief review of the structure of the new coronavirus and how it alters the functioning of the human immune system. Subsequently, we describe the immune changes induced by AIT and how these changes could be favorable or unfavorable in the allergic patient infected with SARS-CoV-2 at a particular point of time during the evolving infection.

Results: We describe how a healthy immune response against SARS-CoV-2 develops, versus an immune response that is initially suppressed by the virus, but ultimately overactivated, leading to an excessive production of cytokines (cytokine-storm-like). These changes are then linked to the clinical manifestations and outcomes of the patient. Reviewing the immune changes secondary to AIT, it becomes clear how AIT is capable of restoring a healthy innate immunity. Investigators have previously shown that the frequency of respiratory infections is reduced in allergic patients treated with AIT. On the other hand it also increases immunoregulation.

Conclusion: As there are many variables involved, it is hard to predict how AIT could influence the allergic patient's reaction to a SARS-CoV-2 infection. In any case, AIT is likely to be beneficial for the patient with allergic rhinitis and/or allergic asthma in the context of the SARS-CoV-2 pandemic as controlling allergic diseases leads to a reduced need for contact with healthcare professionals. The authors remind the reader that everything in this article is still theoretical, since at the moment, there are no published clinical trials on the outcome of COVID-19 in allergic patients under AIT.

(Allergy Asthma Proc 42:187–197, 2021; doi: 10.2500/aap.2021.42.210013)

During the coronavirus disease 2019 (COVID-19) pandemic, groups of different medical specialties

have given specific recommendations related to their area of greatest experience.^{1,2} Similarly, guidelines have been published in relation to allergen immunotherapy (AIT) in times of COVID-19.^{3–6} An interesting finding in the initial epidemiologic reports is that allergy and other conditions with type 2 inflammation do not seem to represent a risk factor associated with severe COVID-19,^{7,8} and analysis of data suggests that the T-helper type 2 (Th2) dominant immune changes secondary to allergic asthma could confer benefit through downregulation of the late-phase hyperinflammation commonly seen with severe respiratory viral diseases, including coronavirus.⁹ To the best of our knowledge, the potential benefit that AIT may have in patients with allergic diseases during the pandemic due to its regulatory response has only briefly been addressed.¹⁰

An exhaustive bibliographic review with regard to the pathophysiology of COVID-19 and the mechanisms of action of AIT was carried out by a special *ad hoc* working group of Mexican allergists/immunologists. As a result, in this review, we included a brief summary of the immunologic changes secondary to the severe acute respiratory syndrome (SARS)

From the ¹Médica Sur, Clinical foundation and hospital, Mexico City, Mexico; ²Centro Universitario de Ciencias de la Salud, Universidad Autónoma del Estado de Hidalgo, Mexico; ³Private practice, Hospital Médica Sur, Mexico City, Mexico; ⁴Universidad Autónoma de Tamaulipas, Matamoros, Mexico; ⁵Departamento de Disciplinas Filosóficas Metodológicas e Instrumentales, Universidad de Guadalajara, Jalisco, Mexico; ⁶Grupo COSTAMED, Playa del Carmen, Mexico; ⁷Facultad de Medicina y Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Monterrey, Mexico; ⁸Servicio de Alergia e Inmunología Clínica, Hospital Infantil de México Federico Gómez, Mexico City, Mexico; ⁹Subdirección de Enseñanza e Investigación, Hospital General de Especialidades Juan María Salvatierra, Baja California Sur, Mexico; ¹⁰División de Medicina, Hospital Juárez de México, Ciudad de México, Mexico; ¹¹Centro de Inmunología, Alergia y Pediatría, Hospital Angeles Lomas, Estado de México, Mexico; and ¹²Hospital General de Zona N. 1, Instituto Mexicano del Seguro Social, Oaxaca, Mexico. D. Larenas-Linnemann and J.A. Ortega-Martell have contributed equally to this article. D. L. L. is a board member and has received grants from Mylan, GK, Boehringer Ingelheim, AstraZeneca, Sanofi, Novartis and UCB. The remaining authors have no conflicts of interest to declare pertaining to this article.

No external funding sources reported

Address correspondence to Désirée E. Larenas-Linnemann, M.D., Hospital Médica Sur, Clinical Foundation and Hospital, Torre 2, cons.602, Puente de Piedra 150, Col. Toriello Guerra, Del. Tlalpan, 14050 Mexico D.F., Mexico

E-mail address: marlar1@prodigy.net.mx

Copyright © 2021, OceanSide Publications, Inc., U.S.A.

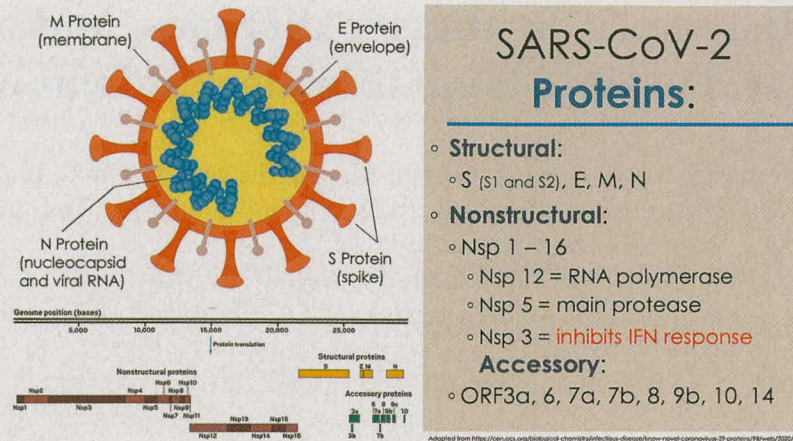


Fig. 1. Getting to know the virus. SARS-CoV-2 has three types of proteins. Among structural proteins, S is subdivided into S1 and S2. The RBD lies in the subunit S1, which binds to the outer surface of the claw-like structure of ACE2. The virus uses the host cell serine protease TMPRSS2 and cathepsin L for its S protein priming, thus preparing the S for membrane fusion. Among NsPs, NsP12 promotes viral gene replication, NsP5 promotes assembly of new virions, and NsP3 inhibits the cell response through interferon production. Among the accessory proteins (ORF), several of them enhance viral replication, whereas others inhibit the antiviral response with interferons. SARS-CoV-2 = coronavirus associated with severe acute respiratory syndrome type 2; S = spike protein; RBD = receptor-binding domain; ACE2 = angiotensin-converting enzyme 2; TMPRSS2 = type 2 transmembrane serine protease; NsP = nonstructural protein; ORF = open reading frame (for antic protein) (RNA_m sequence between a translation initiation codon and a termination codon). The left part of figure 1 is adapted from Katsnelson A. What do we know about the novel coronavirus's 29 proteins? 2020. Available from: <https://cen.acs.org/biological-chemistry/infectious-disease/know-novel-coronaviruss-29-proteins/98/web/2020/04>. Last accessed January 6th, 2021. Adapted from Ref. 68.

coronavirus of 2003 and coronavirus associated with SARS type 2 (SARS-CoV-2) by focusing on the different stages of the immune response against the virus, followed by the effects of AIT on the innate immunity and its possible influence on the morbidity of respiratory infections in patients with allergic diseases. The information presented in this document is up to date at the time of its creation October 2020. However, it must be weighed in the current context in which evidence on this topic is mainly based on preliminary data, and knowledge is advancing with breakneck speed. Thus, it should yet be considered as a “work in progress.” In this review, we did not discuss in detail other coronavirus-related pathological mechanisms that could contribute to multiple organ damage. D.E. Larenas-Linnemann and J.A. Ortega-Martell contributed equally to this article.

SARS-CoV-2 STRUCTURE AND ITS PROTEINS

Studies in human and animal models have demonstrated that SARS-CoV-2 is an RNA virus, with a positive single chain. Its genetic material codifies for 29 proteins: structural, nonstructural, and accessory (Fig. 1). Basically, SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE2), a membrane-bound receptor, for entry and the adjacent serine protease transmembrane serine protease 2 (TMPRSS2) for spike (S) protein priming. The S protein in the viral spike is normally

present as a trimeric; it contains two subunits, S1 and S2, with the former binding to the host receptor, ACE2, and the latter mediates fusion with the host's cell membrane.¹¹ This has led to the hypothesis that known TMPRSS2 inhibitors approved for clinical use (such as bromhexine) might block the priming of SARS-CoV-2 and potentially have antiviral activity.¹²

The interaction between the viral S protein and the host's membrane-bound ACE-2 and TMPRSS2 allows the virus entrance into the upper respiratory airway epithelium and, later on, to the surfactant-generating type II pneumocytes in the lower airway. Both type II pneumocyte destruction and fibrin production exacerbate lung damage once viral pneumonia is present. Moreover, SARS-CoV-2 can infect other organs¹³ as ACE2 and TMPRSS2 messenger RNA (mRNA) has been observed in the heart, digestive tract, liver, kidney, and brain, and in the epithelial cell lining of the nose, trachea, and distal airways.¹⁴ Also, some nonstructural proteins of the coronaviruses (SARS-CoV, coronavirus associated with Middle Eastern respiratory syndrome [MERS-CoV], and SARS-CoV-2) interfere with the antiviral innate immune response, as reviewed below.^{15–17}

IMMUNE RESPONSE TO SARS-CoV2 in the context of cell biology and clinic

In Fig. 2, we present how SARS-CoV-2 can interact with the host when a healthy immune response is

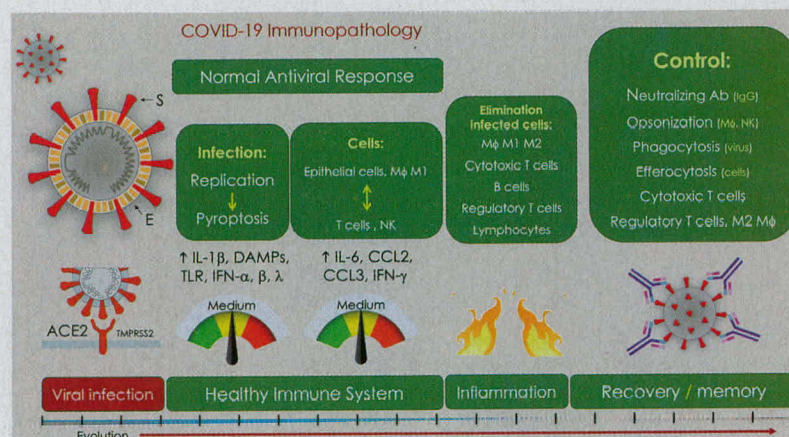


Fig. 2. Healthy antiviral response. SARS-CoV-2 binds to the cells through the ACE2 receptor and cell entrance is supported by cleavage of S protein by TMPRSS2. During viral replication, the cell undergoes changes that lead to death from pyroptosis, and the release of DAMP that, together with PAMP from the virus, activate TLRs and other sensors that induce the production of inflammatory cytokines and type I and III IFNs. In a healthy immune system, the resulting inflammatory response (T cells, NK T cells, IFN- γ , M1 macrophages) eliminates the virus, in a well-controlled manner to not cause further damage (M2 macrophages, Tregs), leaving neutralizing memory antibodies (specific IgG). SARS-CoV-2 = Coronavirus associated with severe acute respiratory syndrome type 2; ACE2 = angiotensin-converting enzyme 2; S = spike; TMPRSS2: type 2 transmembrane seine protease; DAMP = damage-associated molecular pattern; PAMP = pathogen associates molecular pattern; TLR = toll-like receptor; IFN = interferon; NK = natural killer; Treg = regulatory T cell; IgG = immunoglobulin G.

generated, which can help eliminate the virus and produce immunologic memory. An essential part of the initial response to the virus is carried out through the recognition of damage-associated molecular patterns and pathogen-associated molecular patterns through intracellular receptors, with the subsequent production of interferon (IFN) and other proinflammatory cytokines.

During the first phase of a coronavirus infection type I IFN, produced by pneumocytes, epithelial cells, macrophages, and dendritic cells, should play a crucial role in the antiviral defense.^{18,19} However, since the previous SARS-CoV epidemic, researchers have demonstrated dysregulation of the innate immune system, whose activation is initially blocked and delayed by viral evasion mechanisms. Both, SARS-CoV and Middle Eastern respiratory syndrome (MERS) viruses activate mechanisms that impair viral clearance by interfering with the antiviral function of IFNs.¹⁸ These mechanisms can be divided into the following: (a) evasion, when the virus protects itself and its products so that the infected cell does not recognize them as foreign proteins²⁰; (b) suppression of IFN transcription, in which the virus inhibits intracellular activation of IFN transcription^{20–24}; and (c) suppression of IFN signaling, when viral products block IFN receptors and IFN-inducible genes (Fig. 3).^{25–27} With the information generated from the structural studies of the SARS-CoV-2 that causes the COVID-19 pandemic to date, a similar reduction of IFN production seems to be confirmed, although the exact mechanisms are not yet known, and evidence with regard to the functionality of these proteins is still controversial.²⁸ Also, it seems that SARS-

CoV-2 has other added resources to evade or probably directly affect cells of the immune system.

Immunotypes. A study by Mathew et al²⁹ focused on 125 patients hospitalized with COVID-19, revealed that, although cluster of differentiation antigen (CD) 4⁺ and CD8⁺ T-cells were activated in some patients, T-cell responses were limited in others. In many patients, CD4 and CD8 T-cell proliferation (measured by KI-67 increase) and activation (detected by CD38 and human leukocyte antigen-DR co-expression) were consistent with antiviral responses observed in other infections. Plasmablast responses were present in many patients, reaching >30% of the total B cells, which reflected strong acute activation of the B-cell compartment and the subsequent maturation into antibody-producing plasma cells; as such, most patients made SARS-CoV-2-specific antibodies. Two hundred immune parameters were clustered into two major immune response components and a third pattern that lacked robust adaptive immune responses, which revealed immunotypes of COVID-19.

It is most likely that, due to this initial suppression of the immune response, the first days after infection, the patient is asymptomatic (Figs. 2 and 3), but, even so, contagious, shredding large amounts of viral particles. However, in advanced stages, the same IFNs that were first repressed are now released from various cells.³⁰ At this later stage, viral replication is not the prime pathologic mechanism any more. Instead, the hyperactivation of the immune response is now causing the major damage, as was skillfully reviewed by Bellanti³¹; at this point,

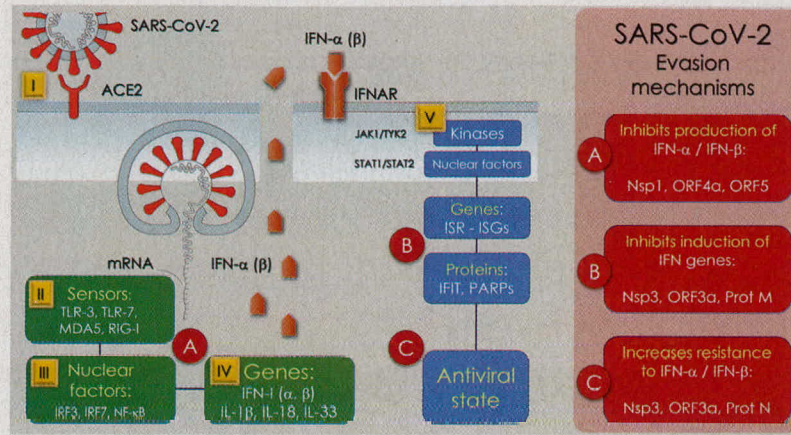


Fig. 3. (A-C) Antiviral response with IFNs and evasion mechanisms of coronavirus. When viral proteins and their genetic material enter into the cell (I), they are recognized by different membrane (TLR3, TLR7), and intracytoplasmic (RIG-I, MDA5) sensors (II), activating nuclear factors (III) that induce transcription of type I IFN and proinflammatory cytokine genes (IV). Subsequently, type I IFNs (α and β) act through their receptor kinases and nuclear factors to induce the activation of genes that produce proteins with antiviral effect (V). SARS-CoV-2 can inhibit IFN synthesis or expression of IFN-induced genes or increase resistance to the effects of IFNs. IFN = Interferon; TLR = toll-like receptor; RIG-I = inducible gene of type I retinoic acid; MDA5 = protein associated with melanoma differentiation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ACE2 = angiotensin-converting enzyme 2; IRF = interferon regulatory factor; ISG = interferon simulator gene; IFIT = interferon-induced proteins with tetratricopeptide repetition; NF- κ B = nuclear enhancer factor of the light κ chains of activated B cells; Nsp = nonstructural protein; ORF = antic proteins for open reading frame.

an increase in the production of cytokines, such as interleukin (IL) 1β , IL-6, IL-8; CXCL ligand chemokine 10; and tumor necrosis factor α , from type II pneumocytes, has been demonstrated.^{32,33} This is generally known as the “cytokine storm,” although the magnitude of the rise in these cytokines in COVID-19 is 100-1000 times lower than the levels seen in real cytokine storm syndromes.³⁴

A cross-sectional study showed that the blood of convalescent patients with moderate-to-severe COVID-19 exhibited robust memory T-cell responses (detected by CD38 expression) months after infection, even in the absence of detectable circulating SARS-CoV-2 antibodies.³⁵ Many T cells also expressed HLA-DR, short for: Marker of proliferation Ki-67, and Programmed cell death protein-1 PD-1, which indicated a combined activation–cycling phenotype. Specific T cells against SARS-CoV-2 generated anamnestic responses to antigens of the internal (nucleocapsid) and surface proteins (membrane and/or spike) in the convalescent phase. Interestingly, the investigators³⁵ also found memory T-cell responses in several healthy blood donors who lacked detectable circulating antibodies against SARS-CoV-2, which implied that seroprevalence as an indicator may underestimate the extent of population-level immunity against SARS-CoV-2. Thus, a previously unanticipated degree of population-level immunity against COVID-19 probably preexists in the T-cell compartment, maybe induced by exposure to other coronaviruses. Future work should have to determine if memory T-cell responses in the absence

of detectable circulating antibodies can protect against severe forms of COVID-19.

Unfortunately, up to 20% of patients who are infected fail to generate an adequate immune response and progress over the following days to severe disease, with rapid progression, often fatal, affecting vital organs (Fig. 4), partly due to the viral activity but mostly due to the hyperactivated host defenses, sometimes accompanied by bacterial superinfection. In patients with severe disease as opposed to patients with mild disease, Meckiff et al³⁶ found increased proportions of cytotoxic follicular helper cells and cytotoxic T-helper cells (CD4-CTLs [cytotoxic lymphocytes]) responding to SARS-CoV-2, and a reduced proportion of SARS-CoV-2 reactive regulatory T cells (Treg). Thus, immune stimulation during the initial stages of the infection and immune regulation in later phases should probably be beneficial.³⁷

INFECTION WITH SARS-COV-2 IN THE CONTEXT OF CELL BIOLOGY AND CLINIC

As for the clinical response to the virus and cell biology, three different stages can be defined 1) early phase, 2) lung damage and 3) overactivation of the immune system with hyperinflammation.³⁸ In Fig. 5, we integrate these stages with the immune changes described above and the potential contagiousness in each stage.

SARS-CoV-2 AND THE AFFECTED ORGANS

The lungs are the main target organs during SARS-CoV-2 infection because the respiratory tract is the

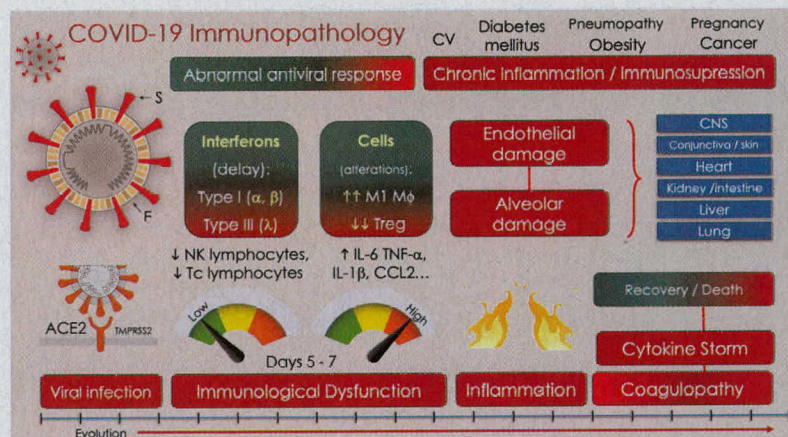


Fig. 4. Abnormal antiviral response. The mechanisms of virus evasion promote immune system dysfunction with a slow and weak initial response (IFN, NK, and cytotoxic T cells), followed by an uncontrolled (low Tregs) and excessive late response (high M1MØ, IL-6), which generates a hyperinflammatory response (cytokine-storm-like) that induces coagulopathy and secondary damage at systemic endothelial level as well as at the alveolar level. Chronic inflammation and/or immunosuppression caused by one or more comorbidities may promote severe multiorgan damage that compromises the patient's life (e.g., cancer, chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised state [weakened immune system] from solid organ transplantation, obesity [Body Mass Index (BMI) of $\geq 30 \text{ kg/m}^2$], serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies, sickle cell disease, type 2 diabetes mellitus). IFN = interferon; NK = natural killer cell; Treg: regulatory T cell; M1MØ = M1 macrophage; IL = interleukin; BMI = body mass index; ACE2 = angiotensin-converting enzyme 2; HTAs = systemic high blood pressure; MfM1 = type 1 transmembrane mitochondrial magnesium transporter; CNS = central nervous system; Tc = cytotoxic T cell; HIV = human immunodeficiency virus.

main entrance pathway of the virus, in addition to the high concentration of ACE2 in type II pneumocytes (Fig. 6). The sensitivity of type II pneumocytes to the virus, due to the expression of ACE2 on their surface, can vary markedly between individuals.³² Interestingly, there is a reduction in the expression of ACE2 on the cell surface after infection with SARS-CoV-2, which results in an enzymic imbalance between ACE, the enzyme that produces angiotensin II (AT-II) and ACE2, the counter-regulatory enzyme. This reduction in ACE2 favors an increase in AT-II, which induces vasoconstriction and hypertension.³⁹ Thus, although ACE2 is the receptor for SARS-CoV-2 and a reduction in ACE2 can be beneficial in the early stages by reducing the gateway to the virus, it can be unfavorable in the more advanced critical phases of the disease, in which the presence of hard-to-control pulmonary arterial hypertension has been documented and ACE2 is necessary to counterbalance ACE and AT-II, which, consequently, makes it difficult to predict if higher or lower baseline concentrations of ACE2 could favor the outcome of COVID-19.⁴⁰ Although the virus is respiratory by origin, the lung is not the only organ that can be affected. Cases with primarily gastrointestinal, skin, or even cerebral symptoms have already been reported.¹³ In addition, there are ACE2 receptors in the endothelium, whose cells are also affected in a large number of patients with severe COVID-19. This is one of the reasons why the respiratory picture can be complicated by injury to the circulation and coagulation.

RISK FACTORS IN SARS-CoV-2 CASE SERIES

Depicted in the upper part of Fig. 4 are the plausible COVID-19 risk factors. Theoretically, pathologies that cause immunosuppression or damage to respiratory mucosa or the endothelium may have a higher risk to evolve unfavorably. Yet, with the present data, it is still preliminary to draw solid conclusions, and it also seems that SARS-CoV and MERS data cannot be fully extrapolated. To date, there are two large COVID-19 case series. In the first study, of 44,672 cases in China, Wu and McGoogan⁴¹ showed that, among the deceased, 10.5% had had cardiovascular pathology, 7.3% diabetes mellitus, 6.3% chronic respiratory pathology (without differentiating between chronic obstructive pulmonary disease [COPD] and asthma), and 6% systemic high blood pressure. However, the report does not mention the percentages of these pathologies in the general population.

In the second study, preliminary data from the U.S. Centers for Disease Control and Prevention,⁴² that sampled approximately 10% of the American population, reported comorbidity in 157 of 178 patients hospitalized for COVID-19 pneumonia (49.7% with hypertension, 48.3% with obesity, 28.3% with diabetes mellitus, 27.8% with cardiovascular disease, 17% with asthma, and 10.7% with COPD), with percentages higher than the numbers of national population statistics. In the most recent U.S. prevalence data

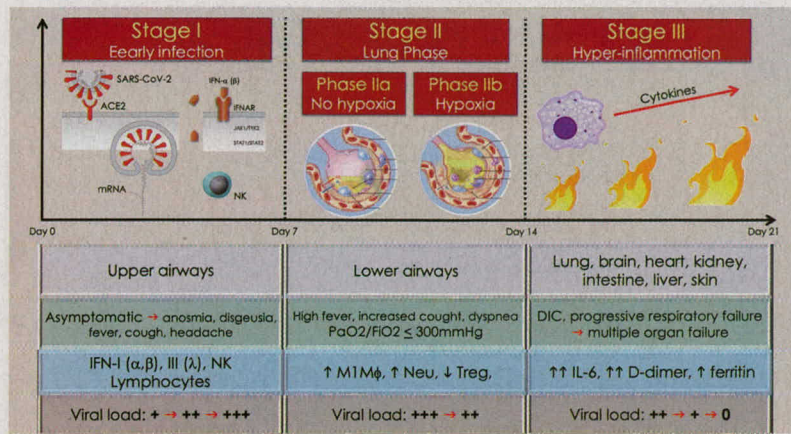


Fig. 5. Evolution of COVID-19. During the first stage the infection manifests itself only in the upper airways and can then progress to the lower airways and spread to other extrapulmonary organs. The pulmonary phase often occurs in the second week causing increasingly intense hypoxia and in the third week the hyperinflammatory phase is frequently accompanied by DIC and can evolve into multiple organ failure. COVID-19 = Coronavirus disease 2019; DIC = disseminated intravascular coagulation; IFN = interferon; IL = interleukin; NK = natural killer cell; Treg = regulatory T lymphocyte.

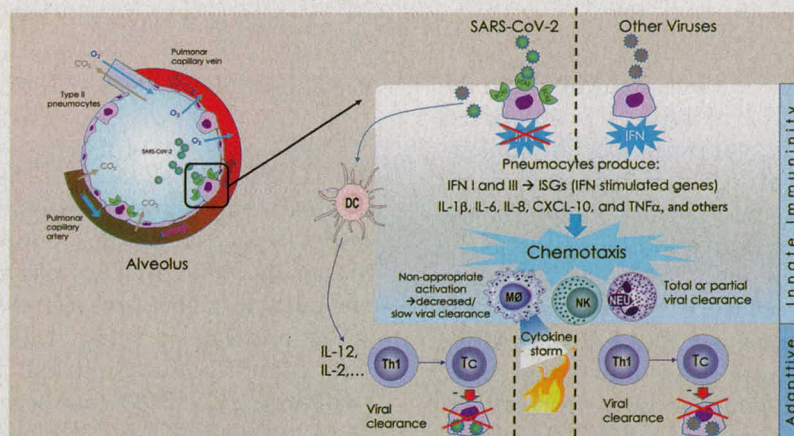


Fig. 6. Alveolar damage. SARS-CoV-2 infects type I pneumocytes and especially type II at the alveolar level, entering the cells through ACE2, thus affecting surfactant factor production. In the normal response against other viruses proinflammatory cytokines are produced that help the total or partial clearance of the virus. In SARS-CoV-2 infection, the initial inflammatory response is poor, whereas, in patients who are critically ill, it becomes excessive (cytokine-storm-like), causing alveolar damage, with inappropriate gas exchange and oxygenation. SARS-CoV-2 = coronavirus associated with severe acute respiratory syndrome type 2; ACE2 = angiotensin-converting enzyme 2; CXCL = CXC ligand chemokine; IFN = interferon; ISG = interferon simulator gene; Th = T helper cell; Tc = cytotoxic T lymphocyte; TNF = tumor necrosis factor. The left part of figure 6, adapted from the alveolar drawing is an idea adjustment from a wikipedia drawing: https://en.wikipedia.org/wiki/Pulmonary_alveolus#/media/File:An_annotated_diagram_of_an_alveolus.svg. Adapted from Ref. 69.

“asthma (moderate-to-severe)” was rated down from “risk” to “possible risk” factor for COVID-19.⁴³ Also, a recent metanalysis could not conclude that asthma was a risk factor.⁴⁴ It was speculated that inhaled corticosteroids could even protect against COVID-19, yet this has been unproven in observational data from almost a million patients with asthma or COPD in the United

Kingdom.⁴⁵ In relation to pregnancy, in which an immune tolerance state occurs with decreased Th1 and increased Th2 responses, previous coronavirus epidemics had been more aggressive^{46,47}; however, the evolution of COVID-19 in 119 pregnant women hospitalized for pneumonia was similar to that of women who were not pregnant,⁴⁸ consistent with preliminary U.S. data.⁴⁹ This

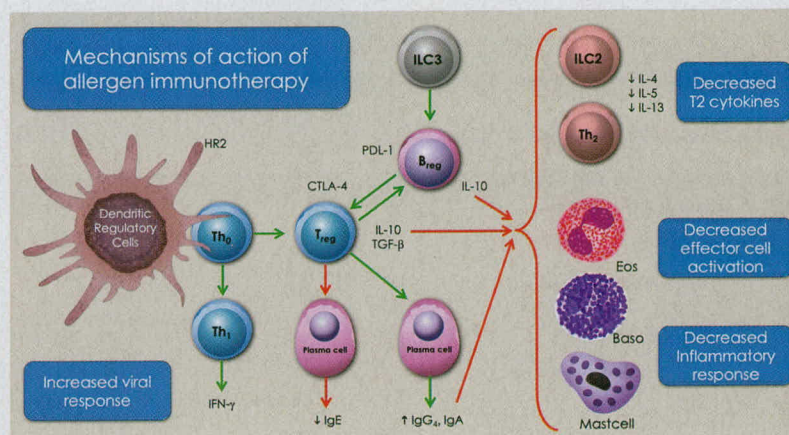


Fig. 7. Mechanisms of action of immunotherapy. The presentation of allergens through regulatory dendritic cells favors the induction of regulatory cells (Treg, Breg) that produce anti-inflammatory cytokines (IL-10, TGF- β). These will decrease the inflammatory response and production of type II cytokines. The production of IFN- γ by Th1 cells will also promote an antiviral state. Adapted from Ref. 57. Treg = Regulatory T cell; Breg = regulatory B cell; IL = interleukin; TGF = transforming growth factor; Th1 = T-helper type 1.

could possibly be explained by the enhanced tolerance, reducing hyperactivation states.

IMMUNOLOGIC CHANGES IN ALLERGIC DISEASES AND ASTHMA AND SUSCEPTIBILITY TO COVID-19

Although respiratory allergies are generally linked to an augmented frequency of viral respiratory tract infections, allergic rhinitis and allergic asthma seem not to be a risk factor for COVID-19 nor for disease severity.⁵⁰ As a plausible explanation for these observations, investigators demonstrated an inverse relationship between the immunoglobulin E (IgE) level and ACE2 mRNA expression, and a reduced concentration of ACE2 mRNA in swabs of nasal and bronchial epithelial cells in children who were sensitized, which reduced even further after allergen challenge testing.⁵¹ Similarly, in 268 patients with asthma, there was an inverse correlation between Th2 cytokine activity and ACE2 mRNA levels compared with healthy controls.⁵² However, the expression of the serine protease needed for the S-protein cleavage, TMPRSS2, was significantly and positively associated with type 2 cytokines, specifically IL-13.⁵³ Thus, there is clear duality in the context of COVID-19 susceptibility and the immune changes brought about by allergic disorders and type 2, eosinophilic inflammation in asthma.

ALLERGY AND RESPONSE TO VIRAL INFECTIONS: EFFECT OF AIT

Immune Changes Induced by AIT

At first, AIT reestablishes the IFN- α production of dendritic cells, crucial during the initial phases of

innate immunity.⁵⁴ This effect probably enhances the response to infections.⁵⁵ AIT increases IL-35 levels, thus inducing IL-10 production and Tregs (transforming growth factor β^+ CD4⁺CD25⁺) differentiation. Thus, in early stages of AIT, there is an increase in immunoregulation. Exposure to high doses of the allergen restores the regulatory function of dendritic cells, which increases the production of IL-12, IL-27, and IL-10.⁵⁶ Consequently, T cells mature into Th1 or Treg lymphocytes, rather than into Th2 lymphocytes; subsequently, T- and B-regulatory lymphocytes increase the production of IL-10 and transforming growth factor β . AIT also adjusts the memory T and B cells toward a more regulatory pattern.⁵⁷ After several months of AIT, there is an increase in IFN- γ , which comes from Th1 lymphocytes, a rise in the activation threshold that triggers mast cells and basophils, and a reduction in the specific IgE/IgG4 ratio. This has been documented both for the subcutaneous (subcutaneous immunotherapy) as well as for the sublingual route (sublingual immunotherapy) (Fig. 7).^{56,57}

AIT and SARS-CoV-2

At present, to our knowledge, no study has been published on the effect of AIT in patients with COVID-19, nor has literature documented the impact that AIT could have on the prevention or severity of the disease. When reflecting on the immune changes brought about by AIT, however, we and other investigators have speculated on its possible beneficial role.¹⁰ One could speculate that function restoration of various cells involved in the innate and adaptive immune response could have a positive effect on the initial antiviral defense. Furthermore, an increase in regulatory cells and molecules might control the cytokine (IL-6 and

Immunotherapy Changes	COVID-19 Changes	
	Potentially favorable	Potentially unfavorable
1. Reset Dendritic cell function	Antiviral effect (Th1) Tolerance (Treg)	Initial evasion
2. ↓ Activity of mast cells, basophils, eosinophils, ILC2s, Th2 cells	Decreased inflammation	Early: increased ACE2 Late: increase ACE2 expression (↓ IL13 expression)
3. Increases IFN-γ	Increased antiviral IFN-λ	Cytokine storm in late stage
4. Changes Th2 → Treg / Breg	Decreased inflammatory activity	Decreased inflammatory activity
5. Changes Th2 → Th1	Antiviral activity increased Tc	Increased inflammatory activity
6. Increases IL-10 and TGF-β	Decreased inflammatory activity	Initial evasion
7. Changes IgE for IgG4 and IgA	Decreased inflammatory activity	Increase ACE2 expression (↓ IL13 expression)

Fig. 8. Effects of immunotherapy with allergens. The state of tolerance induced by specific allergen immunotherapy can help control an excessive inflammatory response to the virus as well as restore a more effective early antiviral response. Although some of these tolerance mechanisms might enhance the spreading of the virus in an early stage, the other effects (anti-inflammatory and antiviral) are more important to stop tissue damage. Breg = regulatory B lymphocyte; ACE2 = angiotensin-converting enzyme 2; ILC2 = innate lymphoid cell type 2; IFN = interferon; TGF-β = transforming growth factor; Treg = regulatory T cell. Adapted from Ref. 10.

IFN-γ) storm like syndrome in the advanced stages of COVID-19, although the effects of AIT on mononuclear cells, the probable source of these cytokines, has not been elucidated until now (Fig. 8).

With regard to IFN, it could be hypothesized that an increase in IFN-β and IFN-γ could improve antiviral defense. Although AIT mainly increases IFN-γ production, it could probably stimulate the secondary production of other type I (IFN-α and IFN-β) and type III (IFN-γ) IFNs as well. However, some researchers³⁴ have argued that, in advanced COVID-19, an increase in IFN could lead to the deleterious cytokine storm, (previously, IL-6 had already been shown to be part of this phenomenon). Here we would like to point out that the effect of different types of IFNs highly depends on the context, including the presence of other regulatory molecules. Thus, under certain circumstances, IFNs can have a proinflammatory effect and under other circumstances, an anti-inflammatory effect.⁵⁸

VIRAL INFECTIONS, AIT, AND COVID-19

When pondering the current knowledge of the immunologic mechanisms involved in AIT that we have outlined above, we can only theoretically speculate on the effect of AIT on COVID-19. Epidemiologic data on allergies, AIT, and other viral infections could be of use when we try to indirectly extrapolate the potential benefit of AIT in light of the SARS-CoV-2 pandemic. Currently, clinical and population studies^{59–61} indicate that allergy increases the frequency of respiratory infections. As an example, a review of Danish national prescription data bases showed that patients with allergic asthma are more likely to get antibiotics for respiratory tract infections in

comparison with patients with nonallergic asthma. Here, AIT treatment had a protective effect against infections.⁶²

Also, simultaneous exposure to birch pollen and rhinoviruses can weaken the innate immunologic response. *In vitro* tests established a decrease in IFN type I and type III production in both nasal epithelial cells and bronchial cells thus exposed.⁶³ This effect was found in both participants with allergy and healthy participants. Active dendritic cells produce IFN-α, with antiviral and immunoregulatory properties. This capacity of dendritic cells is decreased in patients with allergic asthma.⁶⁴ M1-type macrophages are powerful IFN producers, but this capacity diminishes during rhinovirus-infection-related secondary asthma attacks.⁶⁵

In addition, some studies^{59–61} found that AIT treatment in patients with allergy results in improved allergy control and a decrease in the infection frequency. A review of the German national prescription data⁵⁹ base reported that the use of medications was significantly reduced in patients with allergy who were treated with AIT. Furthermore, AIT decreased drug prescription frequency for patients recently diagnosed with asthma. This effect was still seen 6 years after stopping AIT.⁵⁹ In two prospective case-control studies, it was observed that children treated with sublingual immunotherapy with house-dust mites had significantly fewer respiratory infections (3.5 versus 5.45), antibiotic use ($p < 0.05$), and less fever events ($p < 0.01$) than the controls; these changes were observed as early as 6 months into AIT⁶⁰ and persisted in the measurement at 3 years, in which significantly ($p = 0.01$) fewer episodes of respiratory infections (3.6 versus 5.4), fever ($p < 0.01$), use of antibiotics ($p < 0.05$), and antipyretics ($p < 0.01$) than in children treated only symptomatically without AIT.⁶¹

CONCLUSION

SARS-CoV-2 is an emerging, dangerous virus due to its highly contagious nature and its detrimental effect on several vital organs, such as those in the respiratory and circulatory systems. Furthermore, this virus presents serious challenges by interfering in many different ways with the host's immune response throughout the course of the disease. Due to its novelty and the fact that evidence is still based mainly on preliminary data, we do not yet completely understand the effects that this virus has on the human body, and, currently, it is difficult to predict with certainty the impact that immunomodulatory management with AIT could have on the outcome of COVID-19. We consider that AIT should be continued during the pandemic to better control symptoms and reduce medication in patients with allergy. Also, specifically in patients with asthma, it helps to reduce the frequency of asthma attacks and emergency department visits, which thus reduces possible exposure to SARS-CoV-2⁶⁶; however, apart from these benefits, it is highly likely that a competent innate immune response when coming in contact with the virus could be advantageous as the disease evolves.⁶⁷ However, multicenter prospective studies with solid methodological designs are required to increase our knowledge that concern the effect that AIT has on patients with allergy who are dealing with a SARS-CoV-2 infection.

ACKNOWLEDGEMENTS

We thank the Mexican College of Allergy and Clinical Immunology, the Mexican College of Pediatrics Specialists in Allergy in Clinical Immunology and Allergy, and the Nacional Council of Clinical Immunology and Allergy for their support.

REFERENCES

1. Simone G D. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers 2020. Available online at [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang); accessed March 8, 2021.
2. Larenas-Linnemann D, Del Río Navarro BE, Luna-Pech J, et al. Logistic precautions in preparation and administration of allergen immunotherapy during the COVID-19 pandemic in Mexico. *Rev Alerg Mex*. 2020; 67:199–201.
3. Epstein T, Ponda P, Creticos P, et al. Administration of subcutaneous allergen immunotherapy during the COVID-19 outbreak: a Work Group report of the AAAAI Immunotherapy, Allergen Standardization and Allergy Diagnostics (IASAD) Committee 2020. Available online at https://education.aaaai.org/immunotherapy_covid-19; accessed March 8, 2021.
4. Klimek L, Jutel M, Akdis C, et al. Handling of allergen immunotherapy in the COVID-19 pandemic: an ARIA-EAACI statement. *Allergy*. 2020; 75:1546–1554.
5. World Allergy Organization. Preparing your office for the COVID-19 pandemic 2020. Available online at https://www.worldallergy.org/UserFiles/file/Preparing_your_office_COVID-19.pdf; accessed March 8, 2021.
6. Larenas-Linnemann DE, Epstein T, Ponda P, et al. Gaps in allergen immunotherapy administration and subcutaneous allergen immunotherapy dose adjustment schedules: need for prospective data. *Ann Allergy Asthma Immunol*. 2020;125:505–506.e2.
7. Guan WJ, Liang W-H, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020; 55:2000547.
8. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020; 75:1730–1741.
9. Carli G, Cecchi L, Stebbing J, et al. Is asthma protective against COVID-19? *Allergy*. 2020; 7:10.1111/all.14426. doi: 10.1111/all.14426 [Epub ahead of print].
10. Larenas-Linnemann D, Rodriguez-Perez N, Ortega-Martell JA, et al. Mexican Immunotherapy Working G. Coronavirus disease 2019 and allergen immunotherapy: theoretical benefits invite to adjustments in practice recommendations. *Ann Allergy Asthma Immunol*. 2020; 125:247–249.
11. Dong Y, Dai T, Liu J, et al. Coronavirus in continuous flux: from SARS-CoV to SARS-CoV-2. *Adv Sci (Weinh)*. 2020; 7:2001474.
12. Depfenhart M, de Villiers D, Lemperle G, et al. Potential new treatment strategies for COVID-19: is there a role for bromhexine as add-on therapy? *Intern Emerg Med*. 2020; 15:801–812.
13. Dong M, Zhang J, Ma X, et al. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. *Biomed Pharmacother*. 2020; 131:110678.
14. Glowacka I, Bertram S, Muller MA, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *J Virol*. 2011; 85:4122–4134.
15. Fehr AR, Athmer J, Channappanavar R, et al. The nsp3 macrodomain promotes virulence in mice with coronavirus-induced encephalitis. *J Virol*. 2015; 89:1523–1536.
16. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe*. 2016; 19:181–193.
17. de Lang A, Baas T, Teal T, et al. Functional genomics highlights differential induction of antiviral pathways in the lungs of SARS-CoV-infected macaques. *PLoS Pathog*. 2007; 3:e112.
18. Prompetcha E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol*. 2020; 38:1–9.
19. Cervantes-Barragan L, Kalinke U, Züst R, et al. Type I IFN-mediated protection of macrophages and dendritic cells secures control of murine coronavirus infection. *J Immunol*. 2009; 182:1099–1106.
20. Cardenas WB, Loo Y-M, Gale M Jr, et al. Ebola virus VP35 protein binds double-stranded RNA and inhibits alpha/beta interferon production induced by RIG-I signaling. *J Virol*. 2006; 80:5168–5178.
21. Hiscott J, Lacoste J, Lin R. Recruitment of an interferon molecular signaling complex to the mitochondrial membrane: disruption by hepatitis C virus NS3-4A protease. *Biochem Pharmacol*. 2006; 72:1477–1484.
22. Lin R-J, Chang B-L, Yu H-P, et al. Blocking of interferon-induced Jak-Stat signaling by Japanese encephalitis virus NS5 through a protein tyrosine phosphatase-mediated mechanism. *J Virol*. 2006; 80:5908–5918.
23. Lin R, Yang L, Arguello M, et al. A CRM1-dependent nuclear export pathway is involved in the regulation of IRF-5 subcellular localization. *J Biol Chem*. 2005; 280:3088–3095.
24. Meylan E, Curran J, Hofmann K, et al. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. *Nature*. 2005; 437:1167–1172.
25. Parisien JP, Lau JF, Rodriguez JJ, et al. The V protein of human parainfluenza virus 2 antagonizes type I interferon responses

- by destabilizing signal transducer and activator of transcription 2. *Virology*. 2001; 283:230–239.
26. Rodriguez JJ, Parisien J-P, Horvath CM. Nipah virus V protein evades alpha and gamma interferons by preventing STAT1 and STAT2 activation and nuclear accumulation. *J Virol*. 2002; 76:11476–11483.
27. Taslidere B, Mehmetaj L, Ozcan Ab, Gulen B, et al. Melkersson-Rosenthal syndrome induced by COVID-19: a case report. *Am J Emerg Med*. 2020; 41:262.e5–262.e7.
28. Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*. 2020; 181:894–904.e9.
29. Mathew D, Giles JR, Baxter AE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science*. 2020; 369:eabc8511.
30. Kong SL, Chui P, Lim B, et al. Elucidating the molecular pathophysiology of acute respiratory distress syndrome in severe acute respiratory syndrome patients. *Virus Res*. 2009; 145: 260–269.
31. Bellanti JA. The role of the allergist/immunologist in the COVID-19 pandemic: a Janus-faced presentation. *Allergy Asthma Proc*. 2020; 41:397–412.
32. Qian Z, Travanty EA, Oko L, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome-coronavirus. *Am J Respir Cell Mol Biol*. 2013; 48:742–748.
33. Hsiao C-H, Chang M-F, Hsueh P-R, et al. Immunohistochemical study of severe acute respiratory syndrome-associated coronavirus in tissue sections of patients. *J Formos Med Assoc*. 2005; 104:150–156.
34. Sinha P, Matthay MA, Calfee CS. Is a “cytokine storm” relevant to COVID-19? *JAMA Intern Med*. 2020; 180:1152–1154.
35. Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. *Cell*. 2020; 183:158–168.e14.
36. Meckiff BJ, Ramirez-Suastegui C, Fajardo V, et al. Imbalance of Regulatory and Cytotoxic SARS-CoV-2-Reactive CD4(+) T Cells in COVID-19. *SSRN*. 2020; 25; 183(5):1340–1353. e16.
37. Larenas Linnemann D, Rodriguez-Pérez N, Arias Cruz A, et al. Enhancing innate immunity against virus in times of COVID-19: trying to untangle facts from fictions. *World Allergy Organ J*. 2020; 13:100476.
38. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J*. 2020; 55:2000607.
39. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg(9) bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *Am J Physiol Lung Cell Mol Physiol*. 2018; 314:L17–L31.
40. Chen J, Jiang Q, Xia X. Individual variation of the SARS-CoV2 receptor ACE2 gene expression and regulation. *Aging Cell*. 2020; 19(7):e13168.
41. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323:1239–1242.
42. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 States, March 1–30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69:458–464.
43. CDC 24/7: saving lives pp, (TM). People with Certain Medical Conditions 2020 [updated September 11th, 2020]. Available online at <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html#serious-heart-conditions>; accessed March 8, 2021.
44. Broadhurst R, Peterson R, Wisnivesky JP, et al. Asthma in COVID-19 hospitalizations: an overestimated risk factor? *Ann Am Thorac Soc*. 2020.
45. Schultze A, Walker AJ, MacKenna B, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. *Lancet Respir Med*. 2020; 8(11):1106–1120.
46. Ng PC, Leung CW, Chiu WK, et al. SARS in newborns and children. *Biol Neonate*. 2004; 85:293–298.
47. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: report of two cases & review of the literature. *J Microbiol Immunol Infect*. 2019; 52:501–503.
48. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: a report based on 116 cases. *Am J Obstet Gynecol*. 2020; 223(1):111.e1–111. e14.
49. Curtin S, Abma J. 2010 Pregnancy rates among U.S. women 2015. Available online at https://www.cdc.gov/nchs/data/hestat/pregnancy/2010_pregnancy_rates.pdf; accessed March 8, 2021.
50. Joshi AY, Mullakary RM, Iyer VN. Successful treatment of coronavirus disease 2019 in a patient with asthma. *Allergy Asthma Proc*. 2020; 41:296–300.
51. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma and expression of the SARS-CoV-2 receptor, ACE2. *J Allergy Clin Immunol*. 2020. PMID: 32333915.
52. Bradding P, Richardson M, Hinks TSC, et al. ACE2, TMPRSS2, and furin gene expression in the airways of people with asthma-implications for COVID-19. *J Allergy Clin Immunol*. 2020; 146:208–211.
53. Kimura H, Francisco D, Conway M, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol*. 2020; 146:80–88.e8.
54. Tversky JR, Bieneman AP, Chichester KL, et al. Subcutaneous allergen immunotherapy restores human dendritic cell innate immune function. *Clin Exp Allergy*. 2010; 40:94–102.
55. Shamji MH, Layhadi JA, Achkova D, et al. Role of IL-35 in sublingual allergen immunotherapy. *J Allergy Clin Immunol*. 2019; 143:1131–1142.e4.
56. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol*. 2017; 140:1485–1498.
57. Komlosi ZI, Kovacs N, Sokolowska M, et al. Mechanisms of subcutaneous and sublingual aeroallergen immunotherapy: what is new? *Immunol Allergy Clin North Am*. 2020; 40: 1–14.
58. Cheng Q, Behzadi F, Sen S, et al. Sequential conditioning-stimulation reveals distinct gene- and stimulus-specific effects of type I and II IFN on human macrophage functions. *Sci Rep*. 2019; 9:5288.
59. Wahn U, Bachert C, Heinrich J, et al. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy*. 2019; 74:594–604.
60. Barberi S, Ciprandi G, Verduci E, et al. Effect of high-dose sublingual immunotherapy on respiratory infections in children allergic to house dust mite. *Asia Pac Allergy*. 2015; 5:163–169.
61. Barberi S, Bernardo L, D'Auria E, et al. Allergen immunotherapy and respiratory infections in children: an encouraging experience. *Minerva Pediatr*. 2018; 70:1–4.
62. Woehlk C, von Bulow A, Kriegbaum M, et al. Allergic asthma is associated with increased risk of infections requiring antibiotics. *Ann Allergy Asthma Immunol*. 2018; 120:169–176.e1.

63. Gilles S, Blume C, Wimmer M, et al. Pollen exposure weakens innate defense against respiratory viruses. *Allergy*. 2020; 75:576–587.
64. Edwards MR, Strong K, Cameron A, et al. Viral infections in allergy and immunology: how allergic inflammation influences viral infections and illness. *J Allergy Clin Immunol*. 2017; 140:909–920.
65. Nikonova A, Khaitov M, Jackson DJ, et al. M1-like macrophages are potent producers of anti-viral interferons and M1-associated marker-positive lung macrophages are decreased during rhinovirus-induced asthma exacerbations. *EBioMedicine*. 2020; 54:102734.
66. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA*. 2016; 315:1715–1725.
67. Jensen-Jarolim E, Bachmann MF, Bonini S, et al. State-of-the-art in marketed adjuvants and formulations in allergen immunotherapy: a position paper of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy*. 2020; 75:746–760.
68. <https://cen.acs.org/biological-chemistry/infectious-disease/known-novel-coronaviruss-29-proteins/98/web/2020/04>. Last accessed January 6th, 2021.
69. https://en.wikipedia.org/wiki/Pulmonary_alveolus#/media/File:An_annotated_diagram_of_an_alveolus.svg. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.