Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Asthma-associated risk for COVID-19 development

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The newly described severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a pandemic (coronavirus disease 2019 [COVID-19]). It is now well established that certain comorbidities define high-risk patients. They include hypertension, diabetes, and coronary artery disease. In contrast, the context with bronchial asthma is controversial and shows marked regional differences. Because asthma is the most prevalent chronic inflammatory lung disease worldwide and SARS-CoV-2 primarily affects the upper and lower airways leading to marked inflammation, the question arises about the possible clinical and pathophysiological association between asthma and SARS-CoV-2/COVID-19. Here, we analyze the global epidemiology of asthma among patients with COVID-19 and propose the concept that patients suffering from different asthma endotypes (type 2 asthma vs non–type 2 asthma) present with a different risk profile in terms of SARS-CoV-2 infection, development of COVID-19, and progression to severe COVID-19 outcomes. This concept may have important implications for future COVID-19 diagnostics and immune-based therapy developments. (J Allergy Clin Immunol 2020;146:1295-301.)

Key words: *SARS-CoV-2, COVID-19, asthma, endotypes, type 2 asthma, non–type 2 asthma*

Abbreviations used
ACE-2: Angiotensin-converting enzyme-2
COVID-19: Coronavirus disease 2019
HI: Heterologous immunity
ICS: Inhaled corticosteroid
TMPRSS2: Transmembrane proteases serine 2

GLOBAL EPIDEMIOLOGY

The susceptibility of patients with asthma to COVID-19

First epidemiologic studies of the coronavirus disease 2019 (COVID-19) pandemic in China included 72,314 case records, of which 44,672 were classified as confirmed cases of COVID-19 (diagnosis based on positive viral nucleic acid test result on throat swab samples) and did not identify asthma as a risk factor of severe COVID-19.[1] A total of 548 patients with COVID-19 admitted to Tongji Hospital were retrospectively analyzed and 5 of 548 patients had asthma (0.9%).[2] Zhongnan Hospital of Wuhan University retrospectively analyzed 140 hospitalized patients with COVID-19 and also concluded that allergic disease or asthma is not a risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[3] After 3 months, they had analyzed 290 hospitalized patients with COVID-19 and identified only 1 patient with asthma.[4] A retrospective study of 191 patients with COVID-19 (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) did not report on asthma among comorbidities.[5] The prevalence of asthma in the adult population of Wuhan is 6.4%. The prevalence of asthma among patients with COVID-19 was subsequently reported in several other countries and regions. Studies from Russia, Saudi Arabia, and Brazil confirmed the lower rates of asthma among patients with COVID-19 (1.8%, 2.7%, and 1.5% respectively).[6-8] The prevalence of asthma among patients with COVID-19 in Mexico (3.6%),[9] which like Brazil is also in Latin America, was relatively high compared with that in Brazil. Asthma was not mentioned among the comorbidity list of COVID-19 in a retrospective Indian epidemiological study.[10] In Europe, the prevalence of asthma varied from country to country, with Swedish and Italian cohort studies reporting relatively low rates of asthma, 1.8% and 2.6% (Sweden) and 1.96% and 1.92% (Italy)[11,12] (see Table E1 in this article's Online Repository at www.jacionline.org). Another retrospective case series of 1591 patients hospitalized with laboratory-confirmed COVID-19 in the Lombardy region of Italy did not mention patients with asthma.[13] However, the prevalence of asthma among patients with COVID-19 was higher in Spain, Catalonia, and Ireland (5.2%, 6.8%, and 8.8%, respectively).[14-16] The prevalence of

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asthma in the general population in Italy, Spain, and Ireland is 6.0%, 5.0%, and 7.0%, respectively[12,17,18] (Fig 1, *A* and *B*).[19-26]

However, recent studies from the United States and the United Kingdom indicated high rates of asthma in patients with COVID-19. The prevalence of asthma among patients with COVID-19 was 14.4% versus the national asthma prevalence of 8% to 9% in the United States. Asthma and inhaled corticosteroids (ICSs) were not associated with risk of hospitalization due to COVID-19.[27] A huge retrospective study included 11 acute care hospitals of a public hospital system and described demographic and clinical characteristics and outcomes of patients tested for COVID-19. Of the 22,254 patients who were tested, 13,442 patients tested positive, 6,248 required hospitalization, and 1,724 died. Asthma prevalence rate was 7% among positive patients and 11% among negative patients.[28] A case series of 5700 patients with confirmed COVID-19 in the New York City area provides characteristics of hospitalized patients; asthma prevalence was determined as 9%.[29] The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) study based on 16,749 patients with COVID-19 in the United Kingdom reported about 14% asthma prevalence.[30] A population-based prospective cohort study analyzed data from the UK Biobank and reported about 17.9% prevalence of asthma in patients with COVID-19.[31] Another study that analyzed UK Biobank data reported an asthma rate of about 13% and added that adults with asthma had a higher risk of severe COVID-19.[32] An Australian pediatric study retrospectively included all pediatric patients (aged 0-18 years) who presented to the emergency department of the newly established Respiratory Infection Clinic who tested for SARS-CoV-2 from the day of the first positive confirmed case. One in 4 COVID-19–positive patients had a comorbidity, which was asthma (1 of 4 [25%]).[33] In the group of SARS-negative subjects, asthma was the most common comorbidity, with a prevalence of 11%.[33] The "usual" prevalence of asthma among young Australians aged 0 to 17 years was 10.3% in the period 2017 to 2018.[34]

Overall, in most countries around the world, patients with asthma were not reported with higher rates of COVID-19 infection compared with the general population in the corresponding area. There is a big difference in the incidence of COVID-19 in patients with asthma among different areas and countries, with some of them reporting low rates of COVID-19 with asthma, probably due to the multiple factors including the rigorous self-protection awareness and low proportion of non–type 2 phenotypes.

Severity of COVID-19 in patients with asthma

Except for the susceptibility of patients with asthma to COVID-19, another important issue is whether there is a shift in severity and mortality among COVID-19 patients with asthma compared with those without. Among the 548 patients with COVID-19 admitted to Tongji Hospital, there were 5 with asthma, including 2 of 279 with nonsevere asthma (0.7%) and 3 of 269 with severe asthma (1.1%). There was no significant difference in asthma prevalence between patients with severe and nonsevere COVID-19.[2] Saudi Arabia reported that the prevalence of asthma was 3 (2.9%), 0 (0%), and 1 (7.7%) in patients with mild, moderate, and severe COVID-19, respectively.[7] In the Brazilian retrospective study including 51,770 COVID-19 cases, the prevalence of "moderate to severe asthma" is 1.5%.[8] Asthma was identified in 5.2% of patients with COVID-19 in a Spanish study, with a lower prevalence rate of 3.7% in fatal cases and 5.5% in live discharge case.[14] An Italian study of 355 lethal patients' cases with COVID-19 reported that comorbidities were associated with an increased mortality risk, but asthma was not mentioned on the list of comorbidities.[35] A study conducted in Switzerland included 200 patients with COVID-19 hospitalized in the Lausanne University Hospital and reported 4.0% asthma prevalence, 1 of 37 (2.7%) with asthma among those patients who required mechanical ventilation and 7 of 163 (4.3%) with asthma among those patients who did not require mechanical ventilation.[36] Lieberman-Cribbin et al[37] describe results from the Mount Sinai Health System and found that there was no statistically significant association between asthma status and mortality among patients with COVID-19. Therefore, we provisionally conclude that asthma is not associated with a higher risk of mortality among patients with COVID-19 who have a history of asthma. So far, there is no clear evidence that patients with asthma are more likely to be infected with SARS-CoV-2 or to become severely ill.

The phenotype of asthma patients with COVID-19

Although there is yet little information about asthma phenotypes in patients with COVID-19, we may speculate that patients with asthma with different phenotype hold various susceptibility and severity of COVID-19. The study by the UK Biobank reported that adults with asthma had a higher risk of severe COVID-19, which was driven by the increased risk in patients with nonallergic asthma.[32] In contrast, the risk of severe COVID-19 was not significantly elevated in patients with allergic asthma.

Potential lower risk of patients with type 2 asthma to develop COVID-19

Type 2 asthma is characterized by T_H2-driven airway inflammation with increased levels of IL-4, IL-5, and IL-13 production, blood and airway eosinophilia, and (in the case of allergic asthma) increased levels of total and allergen-specific IgE antibodies associated with mast cell activation. Lymphopenia, particularly due to the reduction of T cells, is a well-established marker for COVID-19 severity, and because patients with asthma with COVID-19 have increased numbers and activation-level T cells and show a less severe course of the disease, it is suggested that both $CD4^+$ and $CD8^+$ T cells reduce the destructive power of SARS-CoV-2.[38] Angiotensin-converting enzyme-2 (ACE-2) serves as a major receptor for SARS-CoV-2 to enter host cells via its structural spike glycoprotein (Fig 2). ACE-2 is predominantly expressed on nasal epithelium, lung, heart, kidney, and intestine, but it is rarely expressed on immune cells.[39,40] Markedly reduced levels of ACE-2 transcripts have been detected in nasal and bronchial epithelial cells of allergy sufferers, and this is associated with allergen exposure, allergen sensitization, and high IgE levels,[41] with lowest levels among patients with both high levels of allergic sensitization and asthma. Conversely, nonatopic asthma was not associated with reduced ACE-2 expression.[41] This is observed in both children and adults with asthma. However, data on the protein level are still lacking.[41] Furthermore, ACE-2 gene expression levels correlate inversely with type 2 biomarkers[42,43] and a functional contribution of these cytokines is indicated because IL-13 reduces ACE-2 gene expression in both the nasal and bronchial epithelium.[41] In addition, ICSs, the first-line anti-inflammatory drug in type 2 asthma, also lower ACE-2 gene expression in sputum.[44]

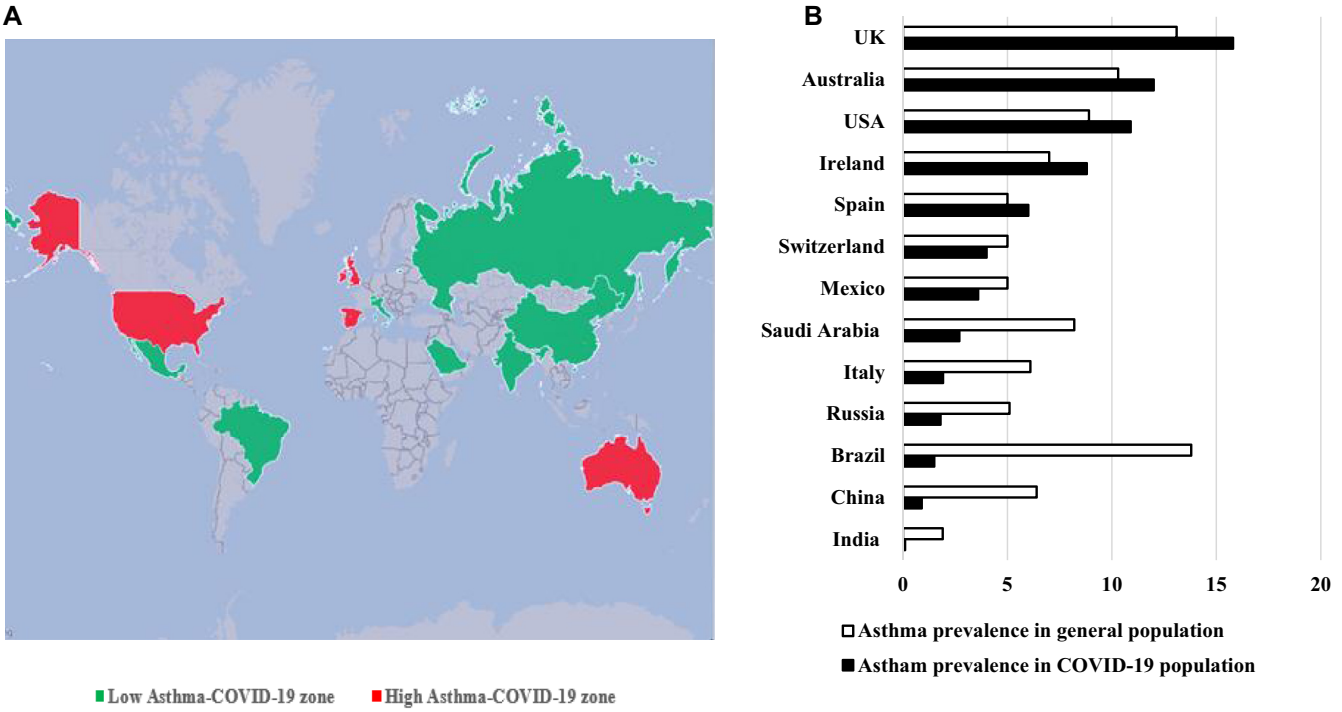

FIG 1. Asthma prevalence. **A,** Countries with high prevalence of asthma among COVID-19 comorbidities in comparison with asthma prevalence in the general population (high asthma-COVID-19 zone) are marked in red color. Countries with low/equal prevalence of asthma among COVID-19 comorbidities in comparison with asthma prevalence in the general population (low asthma-COVID-19 zone) are marked in green. **B,** Asthma prevalence (%) among patients with COVID-19 in comparison with the general population in various countries.[12,17,19-26]

However, there is an increasing amount of data providing evidence that ICSs are associated with reduction in ACE-2 and transmembrane proteases serine 2 (TMPRSS2) gene expression.[44] This presumably occurs by a mechanism independent of any ICS-mediated suppression of T_H2 inflammation. In addition, there is evidence to support that taking ICSs may be beneficial in dealing with coronavirus infections, based on *in vitro* studies with coronavirus application and cytokine production as an outcome.[45]

Host TMPRSS2 cleaves a viral spike protein and facilitates virus fusion to the cellular membrane.[46,47] In contrast to ACE-2, TMPRSS2 gene expression is upregulated under T_H2 conditions.[48] However, there are very few cells coexpressing ACE-2 and TMPRSS2 simultaneously. Therefore, it is questionable whether this increased TMPRSS2 expression favors SARS-CoV-2 infection in patients with allergic asthma.[48]

Blood eosinophilia is an established biomarker for type 2 inflammation,[49,50] and eosinophils have important antiviral properties. This includes single-stranded RNA activating eosinophils via Toll-like receptor-7/myeloid differentiation primary response 88-dependent mechanisms,[51] and eosinophil-derived neurotoxin, which serves as a ribonuclease.[52] Conversely, eosinopenia has been observed in patients with severe COVID-19, and blood cell counts normalize following lopinavir treatment, suggesting that they may serve as a marker for improvement.[3,53,54] In a Russian retrospective study, absolute blood eosinophil counts were below 0.02 × 109/L in 85.7% of patients with asthma, and no patient showed blood eosinophilia.[6]

Infections with respiratory viruses including rhinovirus, respiratory syncytial virus, and influenza virus are major triggers for asthma exacerbation, particularly in children.[55-58] Moreover, asthma has consistently been 1 of the most frequent comorbidities among patients hospitalized because of influenza. In contrast, this is not always the case for SARS-CoV-2. We hypothesize that the main reason for this is a high prevalence of type 2 airway signatures, even in nonatopic children.[48] This could be a major reason why the prevalence of COVID-19 is relatively low in this age group, particularly because allergic, eosinophilic asthma is the major asthma endotype among young patients with asthma. Mast cells also contribute to combat viral infections and, in particular, SARS-CoV-2, because they are a major source of IFN.[59,60]

Potential role of allergen-induced cross-reactive T-cell responses to SARS-CoV-2 among patients with asthma

T-cell responses against SARS-CoV-2 are first detectable approximately 1 week following symptom onset and remain in convalescence, while numbers of virus-specific T cells correlate with neutralization antibody titers.[61] Patients who recovered from SARS-CoV infection developed long-lived virus-specific T memory cells, detectable up to 2 years following infection resolution.[62,63]

Heterologous immunity (HI) has been originally described as a consequence of previous infections, which alter the immune response to a subsequent infection with a different pathogen.[64] This mechanism may occur between closely related or completely unrelated antigens. HI may ultimately alter the outcome of

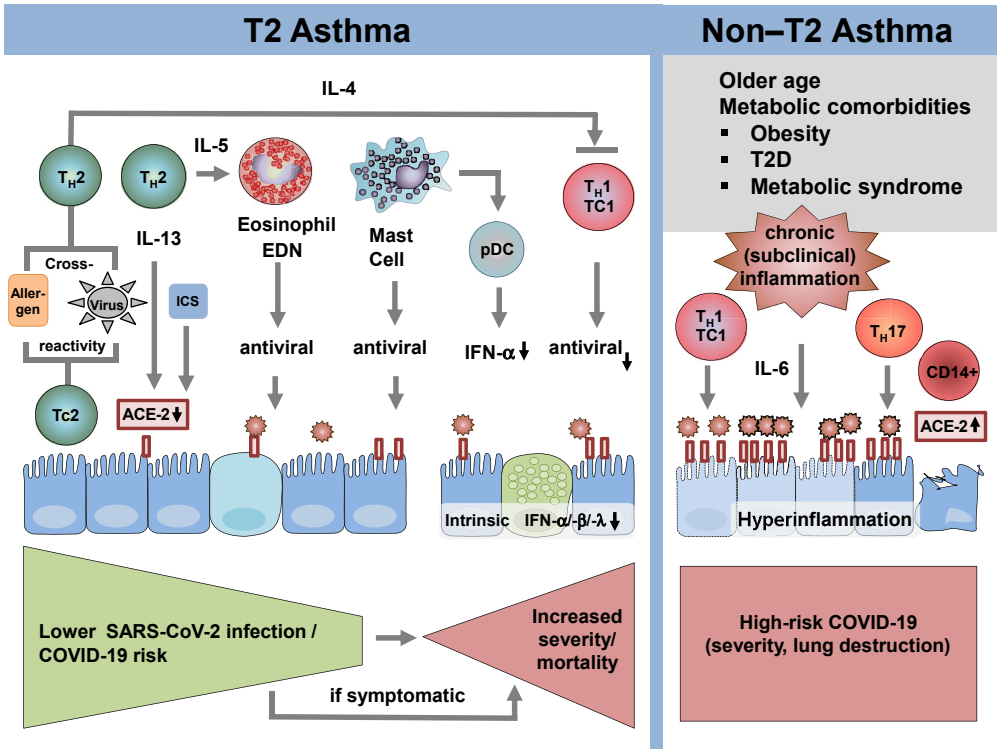

FIG 2. The impact of asthma endotypes on infection of airway epithelium with SARS-CoV-2, development and progression of COVID-19. The 2 major asthma endotypes, type 2 asthma and non–type 2 asthma, are defined by unique inflammatory patterns on the level of adaptive immunity and effector cell responses. Type 2 asthma is characterized by the presence of T_H2 cells secreting IL-4, IL-5, and IL-13. These cytokines have a strong impact on the regulation of helper-cell subsets, airway epithelial function, and regulation of effector cell responses, including eosinophils and mast cells. In contrast, non–type 2 asthma is defined by the presence of T_H1 cells and/or T_H17 cells among other effector T-cell responses. The subset of these patients shows vascular and metabolic comorbidities, which are underlined by the presence of subclinical chronic inflammatory responses (eg, activation of IL-1 signaling pathways). *EDN*, Eosinophil-derived neurotoxin; *pDC*, plasmacytoid dendritic cell; *T2D*, type 2 diabetes.

infections due to cross-reactive recognition and immune protection or due to induction of immunopathology.[65] Cellular-mediated HI may be elicited by means of T-cell receptor cross-reactivity, recognizing similar but distinct antigens or by cytokine-induced nonspecific activation of T cells.[66]

We have previously reported on influenza-induced heterologous immune responses against allergens, which mediated protection from experimental allergic asthma.[67] We recently hypothesized that SARS-CoV-2 may show protein sequence homology to allergens, which may generate cross-reactive T-cell epitopes. We thus applied 2 independent but complementary bioinformatic approaches to identify potentially cross-reactive allergen T-cell and SARS-CoV-2 T-cell epitopes. Our *in silico* analysis revealed numerous candidate epitope pairs, including previously published as well as predicted peptides, and highlighted an important role of MHC class I aeroallergens in this regard[68] (Fig 2). In hosts, who are sensitized to 1 of the predicted allergens, the identified similarities with the SARS-CoV-2 proteome may be protective or harmful. Allergen-specific T cells may develop a memory-type response against heterologous SARS-CoV-2 epitopes, which is by definition faster and more efficient. Quite recently, the role of SARS-CoV-2–specific T cells in exposed and nonexposed individuals has been discussed, which further underlines the potential importance of HI in COVID-19 outcome.[69,70] Specifically, it was suggested that cross-reactive $CD4^+$ T cells in some populations may be recruited into an amplified primary SARS-CoV-2–specific response. Therefore, patients with allergic asthma may carry potential SARS-CoV-2 cross-reactive T cells in their T-cell repertoire if they are sensitized to the respective cross-reactive allergens. This would provide a significant advantage for patients with allergic asthma over other patients with asthma in combating SARS-CoV-2 infections. Further experimental studies are underway to provide supporting functional data and confirm this concept.

Progression of COVID-19 in patients with type 2 asthma

We hypothesize that if SARS-CoV-2 succeeds to establish clinical manifestations in patients with allergic asthma, the risk for disease progression is higher as compared with that in patients with nonallergic asthma with COVID-19. This may occur because of several reasons: (1) T_H2 inflammation counteracts T_H1 immunity and limits the production of proinflammatory cytokines (eg, IL-1β, TNF-α, IL-6, and IL-12), which are required to combat

viral infections; (2) an impaired production of type I and type III IFNs (IFN-α, IFN-β, IFN-λ) by airway epithelial cells has been described in patients with asthma in response to viral infections[71-74]; and (3) plasmocytoid dendritic cells represent the primary source of IFN-α to defend against viral infections and IgE negatively regulates IFN-α production through inhibition of TLR signaling in these cells.[75-78]

COVID-19 in patients with non–type 2 asthma

There is circumstantial evidence that patients suffering from non–type 2 asthma are at a higher risk for progression to severe COVID-19. Non–type 2 is defined as patients with asthma with other inflammatory profile such as T_H1- or T_H17-dominated inflammation including patients with chronic obstructive pulmonary disease and asthma. A recently published nationwide South Korean study reported that among patients with asthma, particularly nonallergic asthma, there is a greater risk of susceptibility to SARS-CoV-2 infection and severe clinical outcomes of COVID-19.[79] Elderly patients with asthma are at a higher risk for morbidity and mortality than younger patients with asthma. In many of these individuals, the inflammatory response is non–type 2-mediated,[80] and the inflammatory endotype is dominated by type 1 and/or type 17 T-cell responses. A molecular phenotype is characterized by inflammasome-associated and metabolic/mitrochrondrial pathways.[81] Many of these patients with asthma suffer from comorbidities including obesity, type 2 diabetes, and hypertension as part of the metabolic syndrome.[82] This endotype is particularly prevalent in inner-city adults[83] and among African Americans.[84]

CD147 activation suppresses several T-cell functions through the inhibition of nuclear factor of activated T-cell pathways.[85,86] CD147 expression correlates positively with body mass index in patients with COVID-19, and is also upregulated by high glycose concentrations.[87] IL-6 serves as a biomarker for systemic inflammation and metabolic dysfunction as well as for severity in these patients with asthma.[88] This subset of patients with asthma may be particularly susceptible to develop severe COVID-19. It is striking that increased cytokine levels with particularly high levels of IL-6 are characteristic for patients with severe COVID-19 as well.[89] It is well established that patients with COVID-19 with these comorbidities are at a higher risk for severity and mortality (L. Qin, C. Zhang, J. Yue, X. Min, unpublished data, 2020). The increased expression of ACE-2 detected in subgroups[41] with type 2 diabetes, chronic obstructive pulmonary disease, African Americans, smokers, and males[44] further contributes to this.[44,90] This may be regulated through IL-17 and supported because of the positive correlation between ACE-2 expression and T_H17 gene signatures.[42] The latter are more frequent among females and based on known age- and sex-induced influences on immune responses, it is likely that such skewing could also take place independently of the presence of asthma.

In contrast to patients with allergic asthma, patients with asthma with this endotype have a low number of blood eosinophils[42] and therefore lack the contribution of these effector cells in anti–SARS-COV-2 defense. CD147, also termed basigin, acts as a receptor for SARS-CoV-2 in T cells and epithelial cells, and humanized anti-CD147 antibody treatment has been shown to reduce inflammation and to improve patients with severe COVID-19.[91-93]

Conclusions

This model may provide a comprehensive explanation for regional differences in asthma prevalence among patients with COVID-19 in North America, Europe, Russia, China, and other nations around the world.

However, to further validate this novel concept, more data and studies are required. Many of the so far published studies are retrospective and are nondiscriminating regarding asthma phenotypes. There is a considerable lack of additional clinical and immunologic parameters. Deep endotyping of patients with COVID-19 and asthma would be required to get a better understanding about the immunologic and metabolic association between these 2 entities. Also, on the level of virus-host interactions with regard to the cellular entry mechanism used by the virus, more data on the transcriptional and translational level of receptor regulation is certainly needed. In addition, there is a lack of longitudinal prospective studies.

A high proportion of patients with type 2 (allergic, eosinophilic) asthma in the population may help to limit SARS-CoV-2 dissemination. However, if patients with allergic asthma develop COVID-19, they may have a higher risk of disease progression. This is mainly due to diminished intrinsic IFN signaling pathways. This might be in contrast to regions with a relatively high population of patients with non–type 2 asthma, which are in particular elderly patients with metabolic comorbidities such as obesity, metabolic syndrome, and glucose dysregulation. This group of patients with asthma has a different inflammatory profile, and due to the chronic subclinical inflammation associated with the metabolic dysregulation, there is circumstantial evidence that the immune system is already (pre-) programmed to develop hyperinflammation in the context of a cytokine storm in association with COVID-19. In both situations, patients with asthma with metabolic dysregulation and patients with COVID-19 with associated hyperinflammation, the IL-6 signaling pathways contribute to the disease among other proinflammatory cytokines.

This concept may illustrate that different asthma endotypes have a differential impact on the infection of airway epithelial cells with SARS-CoV-2, and the development and the progression of COVID-19. This concept requires further clinical and experimental evidence, and we propose to include immunologic endotyping in SARS-CoV-2–infected patients with regard to the presence (or absence) of underlying inflammatory profiles on the level of both innate and adaptive immunity. This could have further implications for immunomodulatory therapies in patients with COVID-19 with asthma comorbidity.

New data are emerging rapidly and deepening our understanding about COVID-19 in patients with asthma/allergy. From the present perspective, current recommendations for treatment of asthma in the context of COVID-19 should not be changed. Patients should receive guideline-based pharmacological treatment including ICSs and biological therapies if needed.

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