

The effect of allergy and asthma as a comorbidity on the susceptibility and outcomes of COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic causes an overwhelming number of hospitalization and deaths with a significant socioeconomic impact. The vast majority of studies indicate that asthma and allergic diseases do not represent a risk factor for COVID-19 susceptibility nor cause a more severe course of disease. This raises the opportunity to investigate the underlying mechanisms of the interaction between an allergic background and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The majority of patients with asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, food allergies and drug allergies exhibit an over-expression of type 2 immune and inflammatory pathways with the contribution of epithelial cells, innate lymphoid cells, dendritic cells, T cells, eosinophils, mast cells, basophils, and the type 2 cytokines interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-31. The potential impact of type 2 inflammation-related allergic diseases on susceptibility to COVID-19 and severity of its course have been reported. In this review, the prevalence of asthma and other common allergic diseases in COVID-19 patients is addressed. Moreover, the impact of allergic and non-allergic asthma with different severity and control status, currently available asthma treatments such as inhaled and oral corticosteroids, short- and long-acting β_2 agonists, leukotriene receptor antagonists and biologicals on the outcome of COVID-19 patients is reviewed. In addition, possible protective mechanisms of asthma and type 2 inflammation on COVID-19 infection, such as the expression of SARS-CoV-2 entry receptors, antiviral activity of eosinophils and cross-reactive T-cell epitopes, are discussed. Potential interactions of other allergic diseases with COVID-19 are postulated, including recommendations for their management.

Keywords: angiotensin-converting enzyme 2, mortality, SARS-CoV-2, susceptibility, severity

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 230 million people with a fatality of over 4.7 million people worldwide (1). Symptoms of COVID-19 are heterogeneous and its severity ranges from asymptomatic, mild, moderate, severe and critical disease to death (2). SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) via its spike protein to enter host cells, and the process of cell entry is promoted by the host transmembrane protease serine 2

(TMPRSS2) that cleaves the spike protein into S1 and S2 fragments, thus enabling cellular membrane fusion (3, 4). Other molecules such as CD147 and CD26 are also potentially used by SARS-CoV-2 as receptors to enter human cells (3, 4). In addition, cell entry of SARS-CoV-2 is pre-activated by proprotein convertase furin, reducing its dependence on target cell proteases for entry (5). Different expression patterns of these receptors in airway epithelial cells, bronchial biopsies and sputum cells have been reported in asthma (6–17).

Asthma and allergic diseases are usually driven by type 2 (T2) immune-inflammatory pathogenic mechanisms, with the contribution of epithelial cells, T2 innate lymphoid cells (ILCs), macrophages, NK-T cells, dendritic cells (DCs), T helper (Th) 2 cells, T cells, eosinophils, mast cells and basophils. Activation of Th2- and ILC2-pathways is at the core of T2 inflammation in asthma (18). T2 cytokines include interleukin (IL)-4, IL-5, IL-9, IL-13 and IL-31, acting in cooperation with epithelium-derived cytokines IL-33, IL-25 and TSLP (18, 19).

Different factors influencing the susceptibility, severity and mortality of COVID-19 have been identified, including demographic characteristics, comorbidities and laboratory indicators (20, 21). A genetic predisposition to any allergic diseases was associated with reduced susceptibility to COVID-19 (22) and atopic status protects COVID-19 patients from severe disease (23). However, conflicting data have been reported about the prevalence of asthma in hospitalized COVID-19 patients. This has led to substantial investigations on the risk of asthma and the different phenotypes of asthma in COVID-19 susceptibility, impacts of asthma on COVID-19 severity and mortality, expression of ACE2 and other entry receptors for SARS-CoV-2 in different tissue and samples from patients with and without asthma and atopy. In addition, the potential impact of other allergic diseases and their treatments such as allergic rhinitis (AR), atopic dermatitis (AD), food allergy (FA) and drug allergy (DA) on COVID-19 have also been investigated. Other studies have focused on the modulation of strategies for the treatment of allergic diseases during COVID-19.

Several risk factors have been identified in the progression of COVID-19 into a severe and critical stage (20, 21). They can be listed as mechanisms that influence anti-viral mechanisms to cope with the virus itself and mechanisms that are responsible for tissue injury and severe disease (24). T2 immunity in allergic diseases and asthma influences many of these factors related to infection and severity of COVID-19 (25). In most cases, these factors act together due to delays or weaknesses in controlling viral replication, increases in the viral load, infection of a higher number of cells and the eventual burden of inflammation and tissue injury. Factors that increase the risk of severe disease include old age, male gender, underlying comorbidities such as hypertension, diabetes, obesity, chronic lung disease, heart, liver and kidney disease, tumors, clinically apparent immunodeficiencies, local immunodeficiencies, such as early type-I interferon (IFN) secretion capacity, and pregnancy (20). The development of a cytokine storm and endotheliitis, together with possible complications including acute respiratory distress syndrome, shock, disseminated coagulopathy, acute kidney injury, pulmonary embolism and secondary bacterial pneumonia, may all underly severe COVID-19 (20). In the current review, we discuss all the aspects of the mutual relationship between asthma and allergies, and COVID-19 pathogenesis.

Asthma and COVID-19

Asthma and COVID-19 susceptibility

On the 19 February 2020, our group reported the clinical characteristics of the first human-to-human contact series in Wuhan, China. Of notice, there were no asthma patients among the 140 hospitalized COVID-19 patients included in the study

(26). A lower incidence of COVID-19 in asthma patients was confirmed by several studies later. Another study in Wuhan reported the prevalence of asthma was 0.9% (5/548) in hospitalized COVID-19 patients (27). In 748 hospitalized COVID-19 patients in Paris, France, 4.8% had a history of asthma (28). Since then, a lower prevalence of asthma in COVID-19 was also reported in Israel (29), Italy (30), Saudi Arabia (31), Mexico (25), Brazil (32), Spain (33, 34) and Russia (35). On the contrary, a higher prevalence of asthma in COVID-19 patients was found in Switzerland (36), Strasbourg (37), France and the UK (14.0–17.9%) (38) at the early stage of the pandemic. A similar prevalence of asthma (6.6%) between COVID-19 patients and the general population (6.4%) was reported in Sweden (39). Conflicting data of asthma prevalence were reported in Korea (40–42) and the USA (43–46). The COVID-19 incidence was not significantly different in active and inactive asthma, suggesting that asthma status does not increase the risk of COVID-19 infection (45). A systemic review reported great variability of asthma prevalence in COVID-19 (1.15–16.9%) (47). This variability of asthma prevalence observed in different countries may be caused by several factors, such as adherence to asthma therapy, control status of asthma, availability of medication, enforcement of lockdown and social distance, prevalence of obesity, diabetes, and other comorbidities and the diagnostic PCR test frequency for SARS-CoV-2 (48). Severe asthma was not regarded initially as a risk factor for SARS-CoV-2 infection (49), even in severe asthma patients requiring ongoing biologic therapy targeting T2 inflammation (50, 51). The reported prevalence of asthma in COVID-19 is listed in Table 1.

Pre-existing asthma and the risk for hospitalization, severity and mortality of COVID-19

Most studies did not identify pre-existing asthma as a risk factor for hospitalization of COVID-19. Asthma did not increase the risk of COVID-19-related hospitalization (43) and the time to resolution of COVID-19 symptoms, particularly lower respiratory tract symptoms (52). A recent study in the USA also confirmed that asthma was not a risk factor for hospitalization of COVID-19 (52). Moreover, allergic asthma was associated with a lower hospitalization risk due to COVID-19 when compared with non-allergic asthma [odds ratio (OR) = 0.52, 95% confidence interval (CI): 0.28–0.91] (52). A multivariate analysis found that asthma patients of male sex, Asian race, and with comorbid chronic obstructive pulmonary disease were associated with increased risk, whereas those solely using short-acting β 2 agonist (SABA) to relieve symptoms were associated with decreased risk for hospitalization of COVID-19 (53). Active asthma and those without medication to control asthma were associated with a higher risk of COVID-19 hospitalization (45). In contrast, the Sweden national cohort identified asthma as a risk factor for hospitalization but not for mortality (39). In a systematic review including 131 studies and 410 382 COVID-19 patients, asthma was not identified as a risk factor for hospitalization (47).

In the UK national multicenter prospective cohort and age-stratified study including 75 463 COVID-19 patients, those with asthma (≥ 16 years old) were associated with a higher risk of receiving critical care including ventilation support and oxygen therapy when compared with those without asthma or

Table 1. Prevalence of asthma in adult COVID-19 patients

Location	Asthma in COVID-19, <i>n</i> (%)	Asthma prevalence in general population (%)	References
Mexico	3.6	5.0	(25)
Wuhan, China	0/140 (0)	6.4	(26)
Wuhan, China	5/548 (0.9)	6.4	(27)
Paris, France	37/786 (4.8)	7.0	(28)
Israel	153/2666 (6.75)	9.62	(29)
Brescia and Verona, Italy	20/1043 (1.92) in Brescia and 6/305 (1.96) in hospitalized COVID-19 patients	6.1 in Brescia, 6.0 in Verona	(30)
Saudi Arabia	4/150 (2.7)	8.2	(31)
Brazil	Moderate-to-severe asthma, 1.5% of 51 700 COVID-19 cases	13.9	(32)
Madrid, Spain	11/189 (5.8)	7.0	(33)
Madrid, Spain	116/2226 (5.2)	7.0	(34)
Russia	23/1307 (1.8)	6.9	(35)
Switzerland	204/2411 (8.5)	2-8	(36)
Strasbourg, France	23/106 (21.7)	7.0	(37)
UK	14.0–17.9	13–13.5	(38)
Sweden	4493/68 575 (6.6)	6.4	(39)
Korea	725/7340 (9.9)	2.2	(40)
Daegu, Korea	3.2% of 2200 COVID-19 patients	2.2	(41)
Korea	96/4057 (2.3)	2.2	(42)
New York, USA	4.4	6.8	(43)
New York, USA	163/1298 (12.6) (<65 years, including children)	6.8	(44)
California, USA	5526/61 338 (9.0), active asthma: 4.5; inactive asthma: 4.5	8.9–10.1	(45)
New York, USA	212/5973 (4.7)	6.8	(46)

other pre-existing respiratory conditions (54). Active asthma was associated with a higher rate of intensive respiratory support and intensive care unit (ICU) admission, especially in patients without medication (45). In patients aged 16–49 years, those with severe asthma [defined as the need for inhaled corticosteroids plus long-acting β_2 agonist (LABA) plus another maintenance therapy] had a significant increased risk of mortality compared with subjects without asthma [adjusted hazard ratio (aHR) 1.17, 95% CI: 0.73–1.86]. Severe asthma patients aged 50 and older were associated with a higher risk of death compared with those asthma patients not requiring therapy (aHR 1.24, 95% CI: 1.04–1.49) (54).

In the above-mentioned systematic review, asthma was not identified as a risk factor of severe disease, ICU admission and intubation, but rather associated with a lower risk of death of COVID-19 [relative risk (RR) 0.65, 95% CI: 0.43–0.98] (47). Other studies found that asthma was not associated with risk of ICU admission and mortality of COVID-19 (46, 55). In contrast, a Korean cohort of 725 COVID-19 patients suggested that asthma was associated with a severe clinical outcome [adjusted OR (aOR) 1.62], which was mainly caused by non-allergic asthma (aOR 4.09) but not allergic asthma (40). This is contrary to another Korean study which showed that asthma was not associated with severe clinical outcomes after adjustment of potential confounding factors (41). Obesity, chronic kidney disease and marital status might be risk factors for ICU admission, and male sex and cardiovascular disease might be risk factors for mortality in COVID-19 patients with previous asthma (53). It is worth noting that these factors are also identified in the general population with COVID-19.

Severe asthma did not increase the risk of severe outcomes of COVID-19, as reported in studies from Italy (49, 56) and the USA (52). Asthma control status was not associated with an increased risk of COVID-19-related death (45). However, patients with severe COVID-19 who were receiving biological

treatment were associated with a higher risk of hospitalization and invasive mechanical ventilation (51). In 50 years and older COVID-19 patients, severe asthma significantly increased the risk of death (aHR 1.96, 95% CI: 1.25–3.08) (54). This discrepancy in results may come from the distinct criteria of severe asthma and the index of outcomes in these studies. On the other hand, available data showed that SARS-CoV-2 did not induce severe asthma exacerbation (37, 57). Studies regarding the impact of asthma on the hospitalization, severity and mortality of COVID-19 are summarized in Table 2.

In children, the prevalence of asthma in COVID-19 patients was lower compared with that in the pediatric population (58–60). Asthma was not associated with increased severity and mortality of COVID-19 (61). On the other hand, improved asthma control and improved lung function were observed in children with asthma during the COVID-19 pandemic, which may be due to reduced exposure to asthma triggers and increased adherence to asthma treatments (62). A general trend of clinical improvement and a reduction in the use of on-demand and basal therapy in allergic children was observed during the lockdown (63). The impact of asthma on COVID-19 and lockdown due to COVID-19 on asthma in children is summarized in Table 3.

The effect of asthma treatments on COVID-19

Several studies on the effect of currently available asthma treatments on the susceptibility, hospitalization, disease severity and mortality of COVID-19 are summarized in Table 4.

Inhaled corticosteroids. Asthma patients on inhaled corticosteroids (ICS) maintenance treatment had a higher expression level of ACE2 in large airway epithelium than those not treated with ICS and healthy controls (64). However, ongoing use of ICS did not increase the risk of hospitalization

Table 2. Impact of pre-existing asthma on the outcomes of COVID-19 patients

location	Impacts of asthma on COVID-19 outcomes	References
Paris, France	Asthma was not associated with increased mortality of COVID-19 (asthma 8.1% versus control 14.6%)	(28)
Strasbourg, France	Asthma did not induce severe COVID-19. aOR, 1.065 (95% CI: 0.272–3.522). And COVID-19 did not induce severe asthma exacerbation	(37)
Sweden	Asthma was associated with increased hospitalization rate but not mortality	(39)
Daegu, Korea.	Asthma was not associated with clinical outcomes of COVID-19	(41)
Korea	Asthma patients older than 50 years (aHR 2.22, 95% CI: 1.03–4.76) and female asthma patients (aHR 3.74, 95% CI: 1.35–10.35) had increased risk of death due to COVID-19	(42)
USA	Asthma was not associated with an increased risk of hospitalization	(43)
New York, USA	In COVID-19 patients <65 years, asthma was not a risk factor for severity and mortality	(44)
California, USA	Active asthma, especially the ones without proper medication, had higher risk of COVID-19-related hospitalization, intensive respiratory support and ICU stay, but had no increased mortality	(45)
Italy	Severe asthma did not increase severe outcomes of COVID-19	(50)
The Netherlands	Severe asthma receiving biologicals were associated with higher risk of hospitalization and intubation	(51)
USA	Asthma was not a risk factor for hospitalization, and allergic asthma was associated with lower hospitalization of COVID-19. Severe asthma did not increase severe outcomes of COVID-19	(52)
USA	Asthma patients solely using SABA to relieve symptoms were associated with lower risk of hospitalization	(53)
UK	Asthma was associated with severe disease; in addition, severe asthma was associated with increased mortality of COVID-19	(54)
Belgium	Asthma was not a risk factor for ICU admission and mortality	(55)
Italy	Severe asthma did not increase severe outcomes of COVID-19	(56)
New York, USA	Asthma was not a risk factor for mortality of COVID-19. OR 0.89 (95% CI: 0.65–1.21).	(58)
Korea	Asthma was associated with severe clinical outcomes, mainly caused by non-allergic asthma.	(40)

Table 3. Interactions of asthma, allergy with COVID-19 in children

Topic	Main findings	References
Prevalence of allergy and asthma in 107 COVID-19 children	The prevalence of AR, asthma, AD and episodic wheezing were 10.3%, 6.5%, 4.7% and 3.7% respectively in pediatric COVID-19 patients. Asthma and allergy are not risk factors for hospitalization of COVID-19.	(58)
182 pediatric COVID-19 cases	Allergy did not impact disease incidence, clinical features, laboratory and immunological findings of COVID-19, and was not a risk factor for infection and severity of COVID-19 in children	(59)
Prevalence of allergy and asthma in 40 COVID-19 children	Prevalence of allergy was 5.0% in COVID-19 children, lower than that in pediatric population (32.2%). Prevalence of asthma was 2.5% and lower than that in pediatric population (11.6%)	(60)
Asthma children with COVID-19	Children with asthma had more symptoms of COVID-19 and higher rate of hospitalization, but no difference in the severity and laboratory findings compared with children without asthma	(61)
Childhood asthma outcomes during COVID-19	Childhood with asthma had a better asthma control and improved lung function during COVID-19, may be due to reduced exposure to triggers	(62)
Children with AR and asthma during COVID-19	A general trend of clinical improvement and a reduction in the use of on-demand and basal therapy in allergic children during the lockdown	(63)

due to COVID-19 in asthma patients (43). In another study, asthma patients on high-dose ICS treatment were found to have a higher death rate for COVID-19 compared with those only treated with SABA (65). Interestingly, in COVID-19 patients aged 50 years and older and with asthma, treatment with ICS alone within 2 weeks of hospital admission was associated with reduced mortality risk compared with those without an underlying respiratory condition (aHR 0.86, 95% CI: 0.80–0.92), and those who were not treated with ICS had no reduction in mortality (54). Considering the fact that an increased risk of death has been demonstrated in the same study in severe asthma patients (ICS+ LABA+ another maintenance therapy) (54) the use of ICS alone may represent a protective effect for COVID-19 mortality. Another study also confirmed that ICS use before hospitalization did not increase SARS-CoV-2 infection (55). In fact, the ICS ciclesonide has been shown to inhibit SARS-CoV-2 RNA replication in cell cultures (66). Studies on the effects

of administration of ICS at an early stage of COVID-19 are controversial and inconclusive (67). In summary, severe asthma, but not ICS, may be associated with an increased risk of worse outcomes in COVID-19 patients with asthma.

Oral corticosteroids. Use of oral corticosteroids (OCS) to relieve the acute exacerbation or reach symptom control without other alternative treatments indicates severe asthma. OCS usage during the last 12 months did not increase the risk of COVID-19 infection in asthma patients (29, 68). However, most studies indicate that OCS usage increased the COVID-19 severity and mortality. OCS usage within 2 weeks prior to hospital admission was associated with a higher risk of death for COVID-19 patients with asthma (HR = 1.25, 95% CI: 1.08–1.44), as demonstrated in the OpenSAFELY study (69). Recent usage (within 120 days), but not former usage of OCS, was a risk factor for the development of moderate/severe

Table 4. Impact of currently available asthma treatments on COVID-19

Treatments	Impacts on COVID-19	References
ICS	Increase ACE2 expression in large airway epithelium	(64)
	Ongoing use of ICS did not increase the hospitalization rate of COVID	(43)
	High-dose ICS treatment was associated with higher death rate of COVID-19	(65)
	Asthma patients older than 50 years and treated with ICS alone within 2 weeks of COVID-19 hospitalization had a reduced mortality compared with those without chronic pulmonary disease	(54)
	ICS use before hospitalization did not increase the risk of ICU admission and death	(55)
OCS	OCS use during the last 12 months did not increase COVID-19 infection	(29, 68)
	OCS use during the last 12 months increased the severity and mortality of COVID-19; recent use (within 120 days) of OCS was a risk factor for COVID-19 severity and mortality	(68)
	OCS use within 2 weeks prior to admission increased the death rate of COVID-19	(69)
	OCS use before hospitalization did not increase the risk of ICU admission and death	(55)
LABA	For asthma patients relying on OCS to control symptoms, OCS may be beneficial	(70)
	No data about LABA use alone on COVID-19	(74)
SABA	ICS+LABA treatment in the last 12 months did not affect the infection, severity and mortality of COVID-19	(43)
	ICS+LABA-treated asthma patients had a higher hospitalization rate than those treated with ICS only and a higher ICU admission rate than those treated without ICS+LABA or with ICS only	(43)
LTRA	SABA use alone for asthma control had no impact on COVID-19 mortality	(54)
	Inhaled SABA only for asthma control in the previous 4 months reduced COVID-19 mortality	(65)
Biologicals	Long-term treatment of montelukast reduced infection and hospitalization rate and clinical deterioration rate of COVID-19	(76)
	Montelukast had no impact on COVID-19 susceptibility	(29)
	LTRA did not increase COVID-19 mortality	(74)
Biologicals	Treatment of severe asthma with biologicals did not increase infection and severity of COVID-19	(79)
	Severe asthma treated with biologicals did not increase the severity and mortality of COVID-19	(68, 80, 81)
	Poor outcomes of COVID-19 in asthma patients treated with biologicals	(51)
	A severe asthma patient treated with Dupilumab had a modest antibody response against SARS-CoV-2	(84)

COVID-19 and the all-cause mortality (68). Another study also demonstrated that OCS usage before hospitalization was associated with increased ICU admission and death in COVID-19 (55).

The benefits of systemic corticosteroids may outweigh the risk of severe COVID-19 outcomes for COVID-19 patients with pre-existing asthma relying on OCS to reach symptom control, (70), e.g., restoring impaired antiviral immunity in asthma (71). Moreover, uncontrolled asthma was associated with increased ICU admission and intensive respiratory support (45), whereas well-controlled asthma was not at increased risk of COVID-19-related death (69). In this context, OCS ought to be continued to maintain asthma control or relieve the asthma exacerbation induced by COVID-19 (72), but with minimal dosage (73).

Long-acting β_2 agonists. As recommended by most asthma guidelines, LABA should not be used in asthma patients without combination with ICS; therefore, there is no evidence about the impact of LABA usage alone on COVID-19 susceptibility and outcomes. Ongoing therapy with combination of ICS and LABA represents a more severe asthma compared with patients on solely ICS treatment. In a UK national cohort study, asthma patients (16–49 years) treated with ICS plus LABA had an HR of 1.02 (95% CI: 0.67–1.54), whereas those treated with ICS plus LABA plus another maintenance therapy had an HR of 1.96 for mortality of COVID-19 (54). In contrast, Korean data involving 218 asthma patients showed that ICS+LABA treatment in the last 12 months did not affect the hospitalization duration, ICU admission and death rates of COVID-19 (74). Asthma patients treated with ICS+LABA had a higher hospital admission rate than those with ICS usage alone, but not those without ICS usage, whereas asthma patients treated with ICS+LABA were associated with a higher

ICU admission rate compared to those without ICS or solely ICS usage (43).

Leukotriene receptor antagonists. The leukotriene receptor antagonist (LTRA) montelukast is a potent inhibitor of the main protease of SARS-CoV-2 (75). In elderly asthma patients, long-term treatment with montelukast was associated with a reduction in infection and hospitalization rate compared to those without montelukast treatment. Montelukast treatment (10 mg/day) also significantly reduced the clinical deterioration rate of COVID-19 (76). The same observation was not found in an Israeli report that montelukast was not associated with decreased infection of COVID-19 (29) and in a Korean study showing that LTRA was not associated with increased mortality in asthma patients (74). Other possible beneficial effects of montelukast to COVID-19 include antiviral properties, prevention of endotheliitis and neurological disorders linked to SARS-CoV-2, improvement of atherogenic vascular inflammation, limitation of the ischemia/reperfusion phenomenon, improvement of respiratory symptoms, limitation of the cytokine storm, mitigation of acute respiratory distress syndrome, antioxidant properties and anti-fibrosis effects, as suggested by Barré *et al.* (77). Nevertheless, further studies are warranted to confirm the beneficial effects of montelukast in the treatment of COVID-19.

Short-acting β_2 agonists. Beta-adrenergic blockers have been suggested to be beneficial for COVID-19 patients as they can potentially reduce ACE2 and CD147 expression, inhibiting inflammation, pulmonary edema, embolism and mucus hypersecretion (78). Thus, β -agonists may be harmful to COVID-19 patients. However, inhaled SABA solely indicates a relatively well-controlled asthma, which is associated with a reduced risk of COVID-19 when compared with uncontrolled

asthma (45). In COVID-19 patients aged 16–49 years, asthma treated with inhaled SABA only was not associated with increased mortality from COVID-19 (HR 0.99, 95% CI: 0.61–1.58) (54). Asthma patients prescribed inhaled SABA only in the previous 4 months had a lower mortality of COVID-19 compared with those prescribed high-dose ICS but had no significant difference in mortality compared with those prescribed low or medium-dose ICS (65). Another Korean study showed that oral SABA in the previous year was associated with an increased medical cost burden in COVID-19 (74).

Biologicals. Biologicals are currently widely used for the treatment of severe allergic or eosinophilic asthma. Data from the Belgian Severe Asthma Registry showed that treatment with biologicals for severe asthma was not a risk factor for SARS-CoV-2 infection nor more severe COVID-19 (79). In severe asthma patients with COVID-19, biological treatment was not a risk factor for COVID-19 (50) or its severity and mortality (68, 80), and there were no significant differences among the different biologic drugs used (80). However, a study conducted in the Netherlands revealed a poor outcome of COVID-19 in asthma patients treated with biologicals (51). Single case reports for asthma patients treated with Omalizumab (81), Mepolizumab (82) and Benralizumab (83) have been reported with a good outcome of COVID-19. Noticeably, a severe asthma patient treated with dupilumab presented with modest antibody response against SARS-CoV-2 (84), suggesting that further studies are needed to elucidate the safety of dupilumab during COVID-19. Delayed and/or impaired type I IFN responses will lead to severe COVID-19 (20), whereas the anti-IgE monoclonal antibody Omalizumab could enhance antiviral responses of plasmacytoid DCs by promoting the IFN production in asthma patients (85). Anti-IL-5/IL-5R treatment reduces eosinophilia, which was identified as a protective factor for COVID-19 infection and severity (86). Nonetheless, further evidence with a large sample size is needed to elucidate the effects of biologicals on the incidence and severity of COVID-19 as well as the serological response in severe asthma patients.

Possible mechanisms underlying asthma and COVID-19 prevalence and severity

Expression of ACE2 and TMPRSS2 in asthma. Reduced expression of ACE2 has been reported in airway epithelial cells and bronchial biopsies from asthma patients (6, 7). On the other hand, increased (8) or unchanged ACE2 expression (9, 10) has also been reported in bronchial biopsies (8, 9) or sputum cells (10) from asthma patients when compared with healthy controls. TMPRSS2 expression in the sputum cells (10) and bronchial biopsies (9) was not significantly different between asthma patients and healthy controls, and there was a positive correlation with the expression of TMPRSS2 and ACE2 (10). Moreover, in asthma patients, male sex, African-American race and history of diabetes mellitus were associated with a higher expression of ACE2 and TMPRSS2, whereas use of ICS was associated with a lower expression of ACE2 and TMPRSS2 in sputum cells (10). In asthma patients, ACE2 expression is decreased in those with

high IgE sensitization or after allergen challenge in nasal and bronchial epithelium (11). In addition, reduced expression and activity of ACE2 were observed in lung tissue of a house dust mite (HDM)-induced mouse model (12). These data suggest that T2 inflammation might have an inhibitory effect on ACE2 expression in airway epithelium. Several studies found that IL-13 significantly reduced ACE2 (7, 11, 13, 14) and increased TMPRSS2 expression in airway epithelial cells (13, 14), and ACE2 expression was negatively associated with, whereas TMPRSS2 expression was positively associated with, T2 cytokines (13, 14). ACE2 expression in the bronchial epithelium was higher in asthma patients with lower peripheral blood eosinophils, an indicator of T2-low airway inflammation. ACE2-high asthma patients were characterized by an overlapping type I and II IFN signature, significant T-cell recruitment and activation in bronchial lavages, and also risk factors for severe COVID-19 such as male gender, hypertension comorbidity and peripheral blood lymphocytopenia (15). A recent study found that ACE2 levels from the sputum of severe asthma patients were significantly higher than that of mild-moderate asthma patients, and TMPRSS2 levels in bronchial biopsies were positively correlated with blood neutrophils (16). This finding may partly explain the worse outcome observed in severe asthma patients.

Expression of other receptors for SARS-CoV-2 in asthma patients. Furin levels are not different in bronchial biopsies between asthma patients and healthy controls (9), but are higher in sputum from severe asthma than from mild-moderate asthma patients, and are positively associated with sputum neutrophils (16). In addition, furin levels in bronchial brushings are positively correlated with blood neutrophils, suggesting that furin may contribute to the increased viral load and outcomes in neutrophilic severe asthma (16).

Basigin (CD147) acts as a binding receptor for the spike protein of SARS-CoV-2. ACE2 and CD147 receptors do not coexist in the airway epithelium, suggesting that CD147 acts as an alternative entry site for SARS-CoV-2 (8). The expression level of CD147 in airway epithelia (8, 17) as well as in blood (8) is not different between asthmatics and non-asthmatics. These data suggest that CD147 does not account for the lower prevalence of asthma in COVID-19.

Antiviral activity of eosinophils. We proposed that eosinopenia can be an early biomarker of COVID-19 (26). In addition, eosinopenia is also a risk factor for severe outcomes of COVID-19, including death (21, 86, 87), especially in those with persistent eosinopenia (21, 86). Eosinophil counts were inversely related to inflammatory markers such as high-sensitivity C-reactive protein (21, 87), blood urea nitrogen (21), liver function and serum amyloid A (21), and positively correlated with lymphocyte count (21, 87). Patients with severe COVID-19 disease had lower eosinophil levels during hospitalization compared with patients with mild or asymptomatic disease, independent of asthma status (52). Eosinopenia is more common in COVID-19 than influenza pneumonia and other pneumonia (86). By contrast, eosinophilia has also been suggested to be a protective factor for SARS-CoV-2 infection in both adults and children (88). Asthma patients with pre-existing eosinophilia (absolute eosinophil count, AEC ≥

150 cells/ μ l) had a lower risk for COVID-19 admission, and asthma patients with eosinophilia during hospitalization due to COVID-19 had lower mortality compared with those whose AEC remained < 150 cells/ μ l (89). Eosinophil cationic protein and eosinophil-derived neurotoxin are eosinophil-derived enzymes that can neutralize the virus (60). The antiviral activity of eosinophils may partly contribute to the lower prevalence of allergic asthma in COVID-19 (90). In asthma patients, eosinophil activation in viral respiratory infections is likely a double-edged sword causing both acute exacerbation of asthma and protection against serious outcomes of viral infection such as SARS-CoV-2 (91). However, no severe outcomes for COVID-19 were reported in patients treated with anti-IL-5R monoclonal antibodies, such as mepolizumab, even with eosinopenia at symptom presentation (92).

Cross-reactive T-cell epitopes between SARS-CoV-2 and allergens. A previous study identified cross-reactive T-cell epitopes between influenza and allergens, which may protect against allergen-induced asthma by CD4⁺ and CD8⁺ effector-memory T cells (93). Similarly, bioinformatic approaches have identified potentially cross-reactive allergen- and SARS-CoV-2 T-cell epitopes, highlighting an important role of major histocompatibility complex (MHC) class I inhalant allergens. These results indicate that asthma patients may be more affected by the heterologous immune response against SARS-CoV-2. In asthma patients sensitized to one of the predicted aeroallergens, the similarities with the SARS-CoV-2 proteome may be protective by preventing an overwhelming type 1 response and the accompanying cytokine storm (94).

Other potential immunological mechanisms. Farne and Singanayagam proposed six rationales to explain the lower prevalence and relatively improved outcome of COVID-19 patients with asthma: 1) lower expression of viral receptors in the airway epithelium of asthma patients; 2) maintenance of ICS confers protection; 3) relatively younger age and/or absence of other comorbidities; 4) chronic inflammation in asthma induces immune tolerance against hyperinflammation; 5) reduced viral exposure because of more strict adherence of social distancing measures by asthma patients; 6) mucus hypersecretion may prevent viral penetration far enough to gain access to airway epithelial cells (95). Of note, the numbers of children admitted to a hospital because of an asthma attack decreased dramatically during COVID-19, and better adherence to ICS, improved air quality and school closure may have contributed to this reduction (96). Mast cells also have high antiviral activity owing to their production of IFNs and other antiviral mediators (57).

AR and chronic rhinosinusitis with nasal polyps

Nasal symptoms in COVID-19 present similarities to those of AR during the pollen season, increasing the complexity of the diagnosis (97). Moreover, the prevalence of the common cold in winter will further complicate the differentiation between perennial AR and COVID-19 (98). Seasonal AR had a higher sino-nasal outcome test-22 score. Blowing of the nose and sneezing were more common and severe in seasonal AR, whereas cough and olfactory disorders were more common

and severe in COVID-19 (99). It is noted that lockdown during the pollen season reduced not only the COVID-19 infection but also the severity of seasonal AR (100).

The prevalence of AR in hospitalized COVID-19 was not higher than in the general population in early reports from Wuhan (9.7%) (26, 101), consistent with a recent finding in Israel (29). However, the data are not consistent with those reported in Korea, where AR was associated with a higher incidence of COVID-19 (40). The same study identified current AR as a risk factor for severe clinical outcomes (OR = 1.40) (40). COVID-19 patients with AR had a higher incidence of asthma than those without AR (101). However, co-existence of AR and asthma was not a risk factor for hospitalization of COVID-19 in children (58).

AR was not a risk factor for hospitalization (43, 102) or longer hospital stay (102) in adults as well as in children (58). This was similar also in other severe outcomes such as severe disease, mechanical ventilation, ICU admission and mortality for COVID-19 patients (102).

The nose is the main entry site for SARS-CoV-2 and so the expression of ACE2 and other SARS-CoV-2 entry receptors has been investigated in nasal tissue biopsies or in *in vitro* cultured human nasal epithelial cells (HNECs). Both the mRNA and protein expression of ACE2 was not altered in nasal tissue of AR patients compared with healthy individuals (101). However, in HNECs, the Th2 cytokines IL-4 and IL-13 reduced ACE2 expression, whilst IFN- α and IFN- γ dramatically increased ACE2 expression (101). In CRwNP patients, a decreased expression of ACE2 and TMPRSS2 was found in olfactory mucosa (103) and a decreased expression of ACE2 in nasal polyps (104). These data indicate a possible protecting effect of T2 inflammation on AR and chronic rhinosinusitis with nasal polyps (CRwNP) patients against COVID-19.

Proper treatment of AR may prevent the spread of SARS-CoV-2 (105). Face masks effectively mitigated the symptom burden in nurses with AR, (106) and thus should be recommended to all AR patients during the COVID-19 pandemic. On the basis of a questionnaire conducted by Allergic Rhinitis and its Impact on Asthma (ARIA) members, intranasal corticosteroids (INCS) can be continued in COVID-19 patients with AR (107). INCS does not prevent the development of olfactory and gustatory dysfunction in COVID-19 patients, however, it may reduce the severity and duration of these symptoms (108). Corticosteroids reduced the expression of ACE2 but not TMPRSS2 in HNECs (109), which also supports the continuation of INCS use in AR patients during COVID-19. Ongoing allergen immunotherapy (AIT) should be continued in AR patients without COVID-19 to avoid deterioration of clinical symptoms during COVID-19 (110). New sublingual immunotherapy (SLIT) but not subcutaneous immunotherapy (SCIT) can be started in selected AR patients (105).

Atopic dermatitis

Limited studies have reported the prevalence of AD in COVID-19. In a Korean national cohort study, AD was not identified as a risk factor for infection and severity of COVID-19 (40). In an Israel study, AD prevalence was also similar between COVID-19 negative and positive individuals (29). Similarly,

AD was not a risk factor for hospitalization of COVID-19 in children (58).

Expression of ACE2, TMPRSS2 and other related molecules in the skin, both from healthy controls and from AD patients, indicates that the skin may be a potential entry site for SARS-CoV-2 (8). No significant difference of ACE2 expression was found among skin tissues from healthy controls, lesional skin and non-lesional skin from AD patients. The expression of TMPRSS2 was higher in non-lesional skin than in lesional skin from AD and in the skin from healthy controls (8). Further research is warranted to elucidate the link between the expression of SARS-CoV-2-related receptors in the skin and skin manifestations of SARS-CoV-2, such as pseudo-chilblains, erythematous maculopapular rashes, vesicular rashes and urticarial rashes (111).

Dupilumab is an anti-IL-4 receptor α monoclonal antibody for the treatment of moderate–severe AD and potentially other T2 inflammations such as allergic asthma and CRwNP. The risk of use of dupilumab during the COVID-19 pandemic has been discussed (112). The European Task Force for AD recommended the continuation of the use of dupilumab in AD during COVID-19 (113), since recent evidence showed that it does not increase the risk of infection and worsen the clinical course of COVID-19 (114). The interruption of dupilumab and other immunomodulatory biologicals has not been suggested because stopping these drugs may exacerbate all T2 inflammation-related diseases such as AD, asthma, AR and CRwNP (113). The effect of dupilumab on the expression of ACE2 and other entry receptors for SARS-CoV-2 as well as the immune responses to SARS-CoV-2 infection needs to be further investigated. Other medications used for the treatment of AD, including topical steroids and calcineurin inhibitors, did not increase the severity of COVID-19 (115).

Food allergy

No patients with a history of FA were reported in our first 140 cases of COVID-19 in Wuhan (26). Interestingly, atopy (defined as those with eczema, AR and FA) was associated with a lower hospitalization rate for COVID-19 patients (116). In children, food allergen sensitization did not increase the hospitalization rate due to COVID-19 (58). To the best of our knowledge, the expression of ACE2 and other SARS-CoV-2 receptors in FA patients has not been reported to date nor the outcome of COVID-19 patients with FA. The COVID-19 pandemic and self-isolation/quarantine have been reported to have a negative impact on the quality of life of children and adolescents with FA because of the limitation in the available medical care and accessing ‘safe’ food (117). However, an Israeli survey found that the reported food allergic reactions during COVID-19 lockdown were lower than those in the previous 3 months. Young age, history of allergic reactions and allergy to multiple allergens were identified as risk factors for FA in preschool children (118). Proper management of FA during COVID-19, including FA diagnosis, FA prevention, management of anaphylaxis, oral food challenge and oral immunotherapy, has been discussed elsewhere (119).

Drug allergy

Sixteen COVID-19 patients with a self-reported history of DA have been reported in our 140 cases (26). A systemic cytokine

storm was suggested to promote activation of monocytes, macrophage and cytotoxic CD8⁺ T cells in severe COVID-19 patients, which in turn may impact the development of maculopapular drug rashes (MDR) (120). Skin biopsies might be necessary to differentiate viral exanthem from drug-induced exanthem in COVID-19 patients (121). No SARS-CoV-2 was detected in skin biopsies of MDR in COVID-19 patients (120). However, to the best of our knowledge, there are no reports on the expression of ACE2 and other SARS-CoV-2 receptors in DA patients, and the outcome of COVID-19 patients with DA. Most of the treatments for COVID-19 are adapted from those for influenza or acquired immunodeficiency syndrome, albeit none of these treatments proved effective in clinical trials. A comprehensive review highlighted published information on the diagnosis and management of drug hypersensitivity reactions to current and candidate off-label drugs for COVID-19 and relevant recommendations (122). Only those with a history of hyperreactivity to vaccines may be excluded from COVID-19 vaccination. Strategies to prevent, diagnose and manage severe allergic reactions to COVID-19 vaccines have been stated in The European Academy of Allergy and Clinical Immunology (EAACI) position papers (123–125) (Table 5) and so will not be discussed in this review.

Chronic urticaria

The COVID-19 pandemic has a critical impact on patients with chronic urticaria (CU), including reduced patient referrals and clinical hours, and a shift towards telecommunication between the patient and physician. Moreover, cyclosporine and systemic corticosteroids, but not antihistamines or omalizumab were less used during the COVID-19 pandemic. CU does not seem to affect the disease course of COVID-19; however, CU exacerbation was reported in almost one-third of patients with COVID-19 (126). Omalizumab is approved for the treatment of chronic refractory urticaria. A recent report suggests that Omalizumab did not worsen the disease course of COVID-19 in seven cases with chronic spontaneous urticaria (127). The risk of discontinuation of Omalizumab on the susceptibility and disease course of COVID-19 was not reported. Omalizumab has been reported to be used to prevent anaphylactoid reactions related to COVID-19 vaccines (128).

Allergen immunotherapy and COVID-19

AIT reduces Th2 responses and induces Treg- and Breg-cell responses. As there is a potential protecting effect driven by a Th2 response and inflammatory cytokine storm associated with Th1 responses in COVID-19, AIT should be discontinued in confirmed COVID-19 patients (73, 129). AIT, both SCIT and SLIT, should be continued in non-infected individuals during the COVID-19 pandemic (129), since delayed SCIT with aeroallergen during the COVID-19 pandemic resulted in deteriorated symptom scores and life quality of AR and asthma (110). In patients recovered from COVID-19 or with a sufficient SARS-CoV-2 antibody response after (asymptomatic) disease, AIT can be started or continued as planned (129). There are no reports on whether a history of AIT will reduce the risk of infection and severe outcome in COVID-19 patients with AR and/or allergic asthma.

Table 5. EAACI position papers on the management of allergic diseases during COVID-19

Allergic disease or topics	Recommendations	References
Asthma	ICS or OCS should continue. Spacers of large capacity are recommended to replace nebulizer for active infectants	(72)
Intranasal corticosteroids in AR in COVID-19	In COVID-19 patients, intranasal corticosteroids (including spray) can be continued in AR at the recommended dose	(107)
Drug allergy	All available information about drug hypersensitivity reactions due to current and candidate off-label drugs to treat COVID-19	(122)
Severe allergic reactions to COVID-19 vaccines	Milder and moderate reactions should not be excluded from the vaccination; recognize and treat anaphylaxis, including administering adrenalin properly; at least 15 min observation period following vaccination; AR and asthma are not at higher risk of severe allergic reactions to COVID-19 vaccines	(125)
Handling of AIT during COVID-19	Both SCIT and SLIT can be continued in COVID-19 pandemics in uninfected individuals, in suspected individuals with negative test result (RT-PCR) or after an adequate quarantine, or convalescent patients with detection of serum IgG to SARS-CoV-2 without virus-specific IgM	(129)
Managing childhood allergies during COVID-19	Gain the best control of current allergic symptoms and reduce the risk of COVID-19 infection; reduce stress levels of the children and their parents; be aware of the difference of COVID-19 and seasonal allergy; treat allergies according to usual guidelines; recommend using pMDI but not nebulizer	(130)
Biologicals use during COVID-19	Noninfected patients on biologicals for the treatment of allergic diseases should continue their biologicals targeting type 2 inflammation via self-application. In case of an active SARS-CoV-2 infection, biological treatment needs to be stopped until clinical recovery and SARS-CoV-2 negativity is established and treatment with biologicals should be re-initiated	(131)
Organization of an allergy clinic	Recommendations on operational plans and procedures to maintain high standards in the daily clinical care of allergic patients while ensuring the necessary safety measures in the current COVID-19 pandemic	(132)
Management of chronic rhinosinusitis during COVID-19	Intranasal corticosteroids remain the standard treatment for CRS in COVID-19 patients. Surgery should be reduced to a minimum and preserved for patients with local complications and for those with no other treatment options. Systemic corticosteroids should be avoided. Biologicals can be continued with careful monitoring in noninfected patients and should be temporarily interrupted during COVID-19	(133)

Handling of allergic diseases during COVID-19

Different guidelines and position papers have been released by the EAACI to address COVID-19 issues on pediatric allergy management, chronic rhinosinusitis and the organization of an allergic clinic. A consensus was reached on the use of intranasal corticosteroids (INCS), systemic corticosteroids, biologicals and surgery by expert allergists (130–133) (Table 5).

Conclusions

Allergic asthma is generally associated with a lower risk of infection, hospitalization, severe course of disease and mortality due to COVID-19. Uncontrolled severe asthma, especially in patients older than 50 years, may result in worse disease outcome. Treatments for asthma, such as ICS+LABA, LTRA, SABA and biologicals, are not associated with worse outcome of COVID-19. Recent usage of OCS and uncontrolled asthma represent risk factors for progression to a more severe disease. Both AR and AD are not identified as risk factors for infection, hospitalization and severe outcomes of COVID-19. There is limited evidence on the risk of FA and DA on the infection and outcomes of COVID-19. Reduced expression of entry receptors for SARS-CoV-2 in airway epithelium, antiviral activity of eosinophils, cross-reactive T-cell epitopes between SARS-CoV-2 and allergens may all contribute to the protective effect of T2 inflammation. COVID-19 may cause acute exacerbation of asthma and sometimes may be complicated with seasonal AR. AIT should be discontinued in confirmed COVID-19 patients and can be resumed in uninfected individuals or those recovered from COVID-19.

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