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ARIA-EAACI statement on Asthma and COVID-19 (June 2, 2020)

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Introduction

A novel strain of human coronaviruses, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named by the International Committee on Taxonomy of Viruses (ICTV) [1], has recently emerged and caused an infectious disease. This disease is referred to as the "coronavirus disease 2019" (COVID-19) by the World Health Organization (WHO) [2].

The US Centers for Disease Control and Prevention (CDC) have proposed that "People with moderate to severe asthma may be at higher risk of getting very sick from COVID-19. COVID-19 can affect your respiratory tract (nose, throat, lungs), cause an asthma attack, and possibly lead to pneumonia and acute respiratory disease." (May 24, 2020). (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/asthma.html) On the other hand, in the UK, NICE proposes rapid guidelines for severe asthma (https://www.guidelines.co.uk/covid-19-rapid-guideline-severe-asthma/455275.article).

An ARIA-EAACI statement has been devised to make recommendations on asthma, and not necessarily on severe asthma, based on a consensus from its members.

Epidemiologic evidence

It is difficult to clearly assess the prevalence of asthma on COVID-19 in many studies since most patients are older adults and probably have multimorbidities. Most studies do not clarify whether asthmatic patients with COVID-19 have isolated asthma or asthma as a multimorbidity, particularly in the context of hypertension, obesity and diabetes. In particular, obesity is a significant risk factor for COVID-19 and its severity [3], and may be intertwined with asthma.

In some studies, showing data mostly on critically ill patients, there does not appear to be an increased prevalence of asthma [4-7]. In Wuhan, the prevalence of asthma in COVID-19 patients was 0.9%, markedly lower than that of the general adult population of this city [8]. Differently, in New York, among 5,700 hospitalized patients with COVID-19, asthma prevalence was 9% and COPD 4.5% [9]. In California, 7.4% of the 377 hospitalized patients had asthma or COPD [10]. The US CDC reported that between March 1st and 30th 2020, among COVID-NET hospitals from 99 counties and 14 states (an open source neural network for COVID-19 infection), chronic lung disease (primarily asthma) was the second most prevalent comorbid condition for hospitalized patients aged 18-49 years with laboratory-confirmed COVID-19 [11]. Among the 17% of COVID-19 positive patients with an underlying history of asthma, the incidence was at its highest in younger adults (27% in the 18-49 year-old group). The UK experience on over 20,133 hospitalized cases shows that 14% of admissions were patients with asthma [12]. in the OpenSAFELY Collaborative Study

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(UK), it was found an increased risk of severe COViD-19 in patients with asthma, including death, in particular related with the recent use of oral corticosteroid [13]. A review with all identified studies up to May 5, 2020 is available [14]. However, low socioeconomic status, obesity, non-white ethnicity, chronic respiratory disease and diabetes had stronger signals.

Some anti-asthma medications, such as ciclesonide, might have a beneficial effect on COVID-19 [15].

Thus, whether patients with asthma are at a higher or lower risk of acquiring COVID-19 may depend on geography, age, other multimorbidities, different air quality [16], genetic predispositions, ethnicity, social behaviour, access to health care or other factors. Moreover, the current information is obtained mainly from hospitalization or intensive care unit data. Real-life data in a non-selected population of asthmatics are needed to better understand the links between asthma and SARS-Cov-2 in terms of both incidence and severity.

Clinical experience

Asthma does not seem to be a risk factor for severe COVID-19 but patients treated with oral corticosteroids may be at higher risk of severe COVID-19 [14]. However, a large study is needed to fully appreciate the relationship between COVID-19 and severe asthma.

According to the IPCRG (International Primary Care Respiratory Group), patients are still struggling to differentiate their symptoms between asthma flare-ups and COVID-19. They may therefore delay seeking care for asthma or COVID-19. Interestingly, clarity does not appear to have improved as the weeks have passed. People have recurrences or waves of repeated symptoms and it is difficult to understand whether the symptoms are related to an asthma exacerbation or to COVID-19.

According to IPCRG, many clinicians tend to prescribe antibiotics to people who they believe are having asthma exacerbations "just to be safe". They focus on the potential infection element of the trigger more than the asthma management itself. It would seem that COVID-19 might exacerbate this behaviour, not improve it.

In areas where COVID-19 is prevalent, GPs are still very concerned about oral – and, to a certain degree, inhaled – corticosteroids, possibly because they used remote models of care. They are reluctant to prescribe higher doses of ICS or OCS as they fear they cannot tell the difference between a flare-up and COVID-19.

Mechanistic studies

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The extent of expression in the upper and lower airways of the SARS-CoV-2 entry receptors, angiotensin-converting enzyme 2 (ACE2) and TMPRSS2, might impact the clinical severity of COVID-19. ACE-2 was found to be decreased in patients with allergic asthma [17] or in those receiving inhaled corticosteroids [18]. These data suggest that this expression may be a potential contributor, among several other factors, to reduced COVID-19 severity in patients with T2 inflammation [17,19] However, ACE-2 expression in asthma patients was increased in African-Americans, in males and in association with diabetes (21).

Finally, a recent study which analysed the nasal transcriptome from 695 children suggested that the strongest determinants of airway ACE2 and TMPRSS2 expression are T2 inflammation and viral-induced interferon inflammation [20]. However, this study specifically showed that T2 inflammation (via IL-13) impacted differentially on ACE2 and TMPRSS2, with a T2-high phenotype being associated with a highly significant decrease in the former and a significant decrease in the latter receptor. Thus, although SARS-CoV-2-specific analyses and experiments are lacking, the differential effects of T2-inflammation on ACE2 and TMPRSS2 reported in this study warrant further research on whether T2-high and T2-low asthma phenotypes may be associated with differential susceptibility to severe COVID-19.

Development of the ARIA-EAACI statement

The first author developed seven recommendations that were sent to 105 experts around the world for comment. 69 answers were received within 48 hours and the comments were considered. Where experts suggested modification of the recommendations, a discussion was initiated and recommendations modified until consensus was reached. After these modifications, a total of 9 recommendations were proposed for a second round. In the second round, 145 experts were invited to comment on and approve or reject the recommendations. 78 answers were received within 48 hours and, when an agreement of over 80/100 was reached, the question was included in the statement.

The same approach was used for the research questions. Two research needs were dropped.

The geographic distribution of the experts is given in Figure 1. They were from 43 countries.

ARIA-EAACI statement (Table 1)

ARIA-EAACI research questions (Table 2)

Conclusion

This view is pragmatic, cautious and based upon expert opinion. However, it is likely to require modifications as further evidence is gathered. These recommendations are conditional and should be adapted regularly on the basis of evolving clinical evidence.

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Table 1: ARIA-EAACI statement

1	In areas where COVID-19 is prevalent, screening protocols for COVID-19 should be applied to anyone having worsening respiratory symptoms, and personal protective equipment should be used.
2	In areas where COVID-19 is prevalent, lung function testing procedures should be postponed if not deemed absolutely necessary; portable personal devices measuring PEF and FEV1 can be used in the meantime to monitor asthma control using the telemedicine approach.
3	In accordance with the Global Initiative for Asthma (GINA) (https://ginasthma.org/recommendations-for-inhaled-asthma-controller-medications/) patients with asthma should not stop their prescribed inhaled corticosteroid controller medication (or prescribed oral corticosteroids)**.** Stopping inhaled corticosteroids may have serious consequences.
4	Long-term oral corticosteroids may sometimes be required to treat severe asthma, and it may be dangerous to stop them suddenly (GINA).
5	Oral steroids should continue to be used to treat severe asthma exacerbations.
6	In patients infected by SARS-CoV-2 (symptomatic or asymptomatic), nebulisation (which increases the risk of deposition of virus into the lower airways) should be replaced by spacers of large capacity.
7	In accordance with the NICE in non-SARS-CoV-2 infected patients, we propose https://www.nice.org.uk/guidance/ng166/chapter/3-Treatment#patients-having-biological-treatment: • To continue biologics because there is no evidence that biological therapies for asthma suppress immunity • If the patient usually attends a hospital for biological treatments, think about if he/she can be trained to self-administer, or could be treated at a community clinic or at home • To carry out routine monitoring of biological treatment remotely if possible
8	**In** SARS-CoV-2 infected patients, in accordance with the EAACI we propose to cease the treatment until resolution of the disease is established. Thereafter, the administration of the biological should be re-initiated.

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Table 2: ARIA-EAACI research questions

	Real-world studies need to be carried out on a large number of unselected patients to assess	
	1	Impact of COVID-19 on asthma control
	2	Impact of COVID-19 respiratory symptoms on severe asthma
	3	Impact of severe asthma on COVID-19 occurrence and/or severity of pneumonia
	4	Impact of multimorbidities on asthmatic patients for the control of asthma during COVID-19
5		Serologic studies should be performed to assess whether seroconversion and its duration differ in asthmatic and non-asthmatic subjects
6		The phenotype of asthma (allergic, neutrophilic, age….) should be studied
7		In adult patients, studies should clarify whether asthmatic patients with COVID-19 have isolated asthma or asthma in the context of multimorbidity, particularly in the context of high blood pressure, obesity and diabetes mellitus
8		Role of pollen season on COVID-19 severity

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System Disorders pending, a patent Mixed Allergen Compositions and Methods for Using the Same pending, and a patent Microfluidic Device and Diagnostic Methods for Allergy Testing Based on Detection of Basophil Activation pending.

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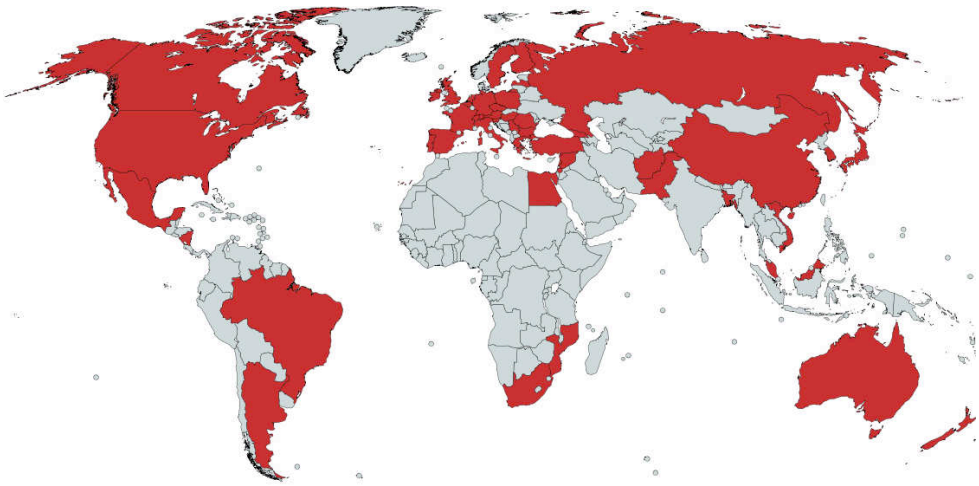
Figure 1: Geographic representation of the experts



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