

# Effectiveness of Inhaled Steroids in Post COVID Cough

Dr. Sudhir Bhandari<sup>1</sup>, Dr. Ajeet Singh<sup>2</sup>, Dr. Govind Rankawat<sup>3</sup>

<sup>1</sup>Senior Professor, <sup>2</sup>Senior specialist, <sup>3</sup>Senior Resident & Corresponding Author,  
Department of General Medicine,  
SMS Medical College and Attached Hospital, Jaipur

## ABSTRACT

**Background:** Coronavirus disease 2019 can lead to persistent cough which may need special attention for better compliance of patients. We aimed to discuss the effect of inhaled steroids (Budesonide) in treatment of post COVID persistent cough and to know the role of inhaled steroids in early recovery of COVID-19 patients.

**Methods:** This retrospective observational case-control study included a total of 120 admitted patients of COVID-19 complaining of persistent cough after exclusion of another known identifiable cause. 60 patients had history of inhaled steroids for treatment of persistent cough while another 60 patients treated with standard of care treatment taken as a control group. The patient's data concerning demography, clinical profile, severity of disease, duration of illness, oxygen support, and outcome were extracted from their medical records. All collected data were tabulated, compiled, and analyzed to establish the possible causality of pneumothorax.

**Results:** Patients of both groups had matched demographic, clinical symptoms, and comorbid status. Patients treated with inhaled steroids along with standard of care treatment had significant fast recovery ( $4.85 \pm 3.94$  days) as compared to control group ( $7.68 \pm 5.43$  days) with  $P=0.0014$ . Patients of inhaled steroids group also had early wean off from oxygen support ( $5.21$  v/s  $7.82$  days), early discharge from hospital ( $6.54$  days' v/s  $8.87$  days), and lesser alleviation of COVID-19 symptoms ( $8.33\%$  v/s  $21.67\%$ ) with  $P<0.05$

**Conclusion:** This study concluded that the inhaled budesonide along with standard of care treatment is helpful to relieve post COVID persistent cough. Beside early relief in cough, inhaled steroids are also useful in early withdrawal of oxygen support and early discharge from hospital.

**Keywords:** COVID-19, Inhaled steroids, Post COVID cough

## INTRODUCTION

The COVID-19 pandemic is the most serious pandemic to have occurred in the last century, with huge mortality and morbidity. The onset of COVID-19 is mild at onset and provides a potential window period to intervene before the development of severe disease<sup>(1,2)</sup>. To date, the majority of studies have focused on investigation and treatment of COVID-19 patients<sup>(3)</sup>. Beside this, there is little knowledge about treatment and prevention of post COVID symptoms especially persistent cough.

Cough is a major symptom of respiratory tract infections and is one of the most common causes to seek medical advice in general practices (GP)<sup>(4)</sup>. Cough can be very bothersome and disabling in daily activities and it significantly impairs the quality of life along with impact on overall physical and psycho-social health of patients<sup>(5)</sup>. Post-infectious cough results from a long-standing inflammation of the bronchial mucosa with open irritant receptors and/or a temporary bronchial hyperresponsiveness<sup>(6,7)</sup>. The post-infectious cough is diagnosed by the patient's clinical history, physical examination and exclusion of other causes such as chronic obstructive pulmonary disease (COPD) or asthma<sup>(8,9)</sup>. Treatment options for symptomatic relief of post-infectious cough in general practice are scarce and inconsistent<sup>(6,7)</sup>.

Two randomized controlled trials (RCTs) assessed inhaled corticosteroids for post-infectious cough<sup>(10,11)</sup>. The trial by Ponsioen et al.<sup>(10)</sup>, which included 135 patients with cough lasting for 2 weeks or more, indicated a potential benefit of inhaled steroids on cough in the overall study population that was explained by beneficial effects in the non-smoker sub-group while in another trial by Pornsuriyasak et al.<sup>(11)</sup> found no benefit of inhaled steroids on cough outcomes at all. A study of COVID-19 showed that patients of bronchial asthma or COPD on inhaled steroids were found to be less present post-infectious cough<sup>(1,2)</sup>. This favors the condition that steroids are helpful in prevention of chronic post-infectious cough<sup>(12)</sup>. In-vitro studies have shown that inhaled glucocorticoids reduce the replication of SARS-CoV-2 in airway epithelial cells,<sup>(13)</sup> in addition to the downregulation of expression of *ACE2* and *TMPRSS2* genes, which are critical for viral cell entry<sup>(14)</sup>. On the other hand, inhaled glucocorticoids also reduce persistent inflammatory activities in post-infectious cough.

Clinical guidelines and recommendations on the use of inhaled corticosteroids are unclear<sup>(6,7)</sup>. A Cochrane review published in 2013 evaluated studies in which inhaled corticosteroids were tested in individuals with post-infectious or chronic cough<sup>(15)</sup>. A majority of the studies focused on patients with chronic cough and only two examined the benefits for post-infectious cough<sup>(15)</sup>. The authors concluded that no recommendation can be proposed due to the high heterogeneity and inconsistency of the studies and their results<sup>(15)</sup>.

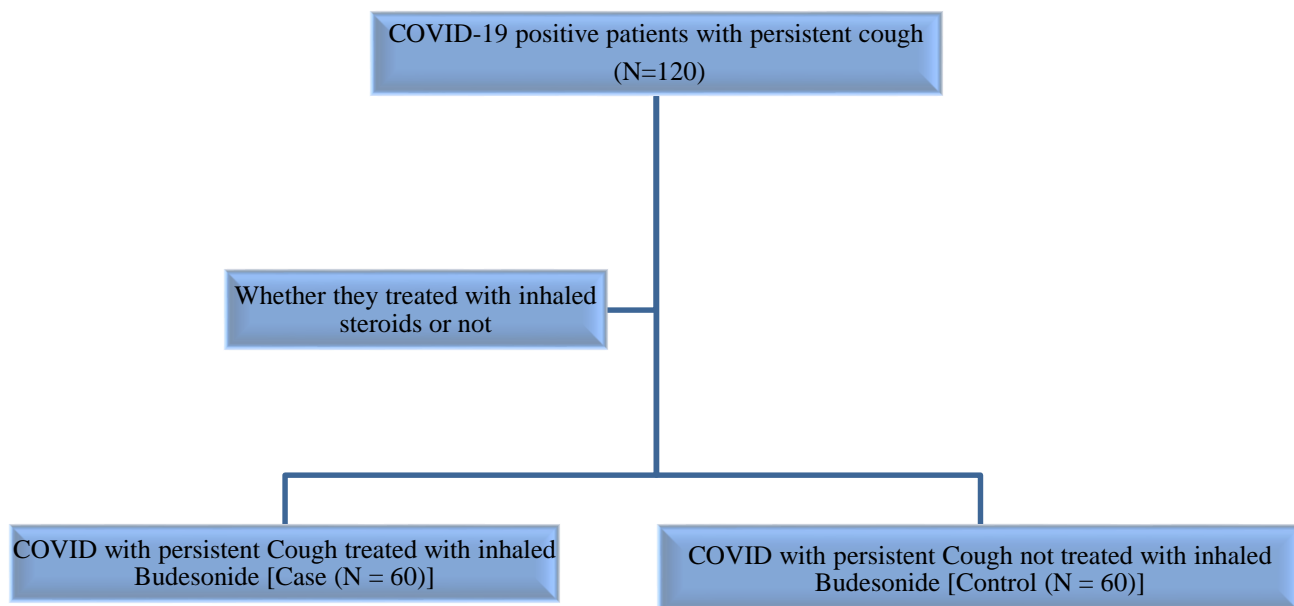
Many of the symptoms in post-infectious cough are thought to be mediated by inflammatory processes that are also present in exacerbations of asthma or COPD<sup>(8,9)</sup>. In these conditions, oral or inhaled corticosteroids were found to be beneficial<sup>(8,9)</sup>. However, at present, treatment of post-infectious cough is still a mystery. There is also considerable uncertainty regarding patient benefits from using inhaled or oral corticosteroids. In this study, we try to find out the role of inhaled corticosteroids (Budesonide inhaler) in suppression of persistent post COVID cough.

## METHODS

**Study Design:** The present retrospective observational case-control study was conducted on 120 COVID-19 positive patients with persistent cough admitted at S.M.S. Medical College and Attached Hospitals, Jaipur, India from 16<sup>th</sup> June 2021 to 15<sup>th</sup> December 2021. This study was approved by the Institutional Ethics Committee of our institute. In this study, we included 60 COVID-19 positive patients with persistent cough who were treated with inhaled budesonide by MDI as case and another 60 COVID-19 positive patients with persistent cough treated with standard of care treatment without any corticosteroids as control. These patients underwent serial observation to collect data till discharge from hospital.

**Data Collection:** COVID-19 was diagnosed based upon World Health Organization interim guidance<sup>(16)</sup>. The patient information about demographic data, medical history, clinical presentation, oxygen support, duration of hospital stay, and final outcome was extracted from the medical records for data analysis. In this study, the severity of COVID-19 patients was decided as per the Indian Council of Medical Research (ICMR) guidelines. Duration of illness and duration of cough were extracted from the medical record. In this study group all COVID positive patients which have persistent cough after illness. Outcome of patients extracted by days on which cough stopped, duration of oxygen support, duration of hospital stays, alleviation of COVID-19 symptoms and COVID-19 related mortality.

For patients of COVID-19 associated persistent cough, we extract data regarding age and gender distribution, disease severity, window period for post infectious cough (time gap between onset of COVID symptoms to onset of persistent post COVID cough), total duration of cough, comorbidity and status of oxygen requirement. All the relevant data compiled, tabulated, interpreted and compared among case with steroids inhalation and control group without steroids inhalation to show role of inhaled steroids in treatment of post infectious persistent cough. Standard of care treatment in both groups is similar and includes antiviral, antibiotics, anticoagulants, bronchodilators, mucolytic, systemic steroids, monoclonal antibody etc. as per indication.



**Statistical analysis:** Quantitative data was expressed as mean and standard deviation. Qualitative data was expressed as proportions. The parameters were compared among different groups using chi-square test and z-score for significant differences. The level of significance was assigned at p-value less than 0.05. Statistical Package for the Social Sciences (SPSS) and R program was used for statistical analysis.

## Results (Table 1 & Graph 1):

A total of 120 COVID-19 patients with persistence cough were included in this study out of which 60 patients treated with inhaled budesonides along with standard of care and another 60 patients treated only with standard of care. In this study, we try to evaluate bit part of inhaled steroids in treatment of persistent cough associated with COVID-19. Hence, we select matched control group to avoid the influence of variable demographic and vital parameters. COVID-19 infected patients with persistent cough, selected for the study group in the range of 28 to 65 years of age. The mean age of COVID-19 patients with persistent cough treated with inhaled budesonide was 47.17 years ( $47.17 \pm 10.21$ ) while in the control group it was 48.05 years ( $48.05 \pm 12.14$ ) without any statistically significant difference ( $p=0.6682$ ). Male patients were affected more in both cases as well as the control group ( $p=0.4593$ ). All selected patients hospitalized with one or more COVID-19 related symptoms. The severity of disease at hospitalization, window period for post-infectious cough, underlying chronic medical illness and required oxygen support was not significantly different in patients treated with inhaled budesonides and control group ( $p>0.05$ ).

Few COVID-19 infected patients of study group deteriorate in the course of disease management. The alleviation of COVID-19 related symptoms was found to be significantly lesser in patients treated with inhaled steroids (8.33%) as compared to patients not

used inhaled steroids (21.67%) for persistent cough ( $p=0.0403$ ). Outcome of study treatment judged by the length of time the cough was stopped. Average time duration to relieve from this disabling symptoms in cases treated with inhaled steroids was 4.85 days while it was 7.68 days in control group which was significantly higher

( $P=0.0014$ ). Post COVID persistent cough relieved early in patients treated with inhaled steroids as compared to control group.

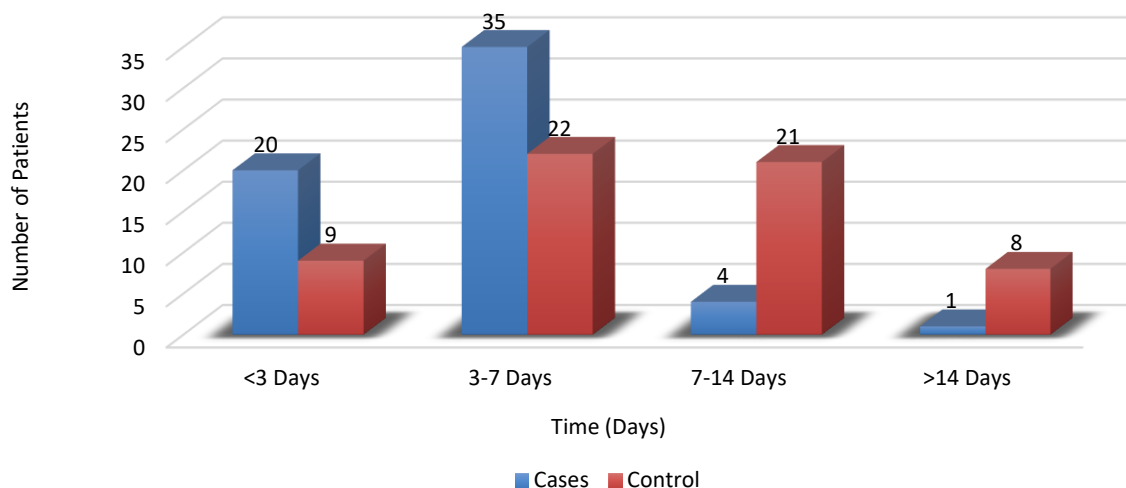
*Table 1: Characteristics of demography, clinical presentation, management and output of COVID-19 patients with persistent cough among cases and control.*

More than 92% patients relieved from cough within one week in cases treated with inhaled steroids while in control group of without inhaled steroids group only 52% patients relieved from cough within one-week duration ( $P<0.05$ ). As per ICMR guidelines,

Characteristics	Case (N=60) (Inhaled Steroids)	Control (N=60) (SOC)	Level of Significance
	Mean $\pm$ SD	Mean $\pm$ SD	
Age	47.17 $\pm$ 10.21	48.05 $\pm$ 12.14	P=0.6682
Gender			
Male	33 (55.00%)	37 (61.67%)	Z=0.7407, P=0.4593
Female	27 (45.00%)	23 (38.33%)	
Disease Severity			
Mild	18 (30.00%)	25 (41.67%)	Z=1.3326, P= 0.1835
Moderate	38 (63.33%)	32 (53.33%)	Z=1.111, P=0.267
Severe	4 (6.67%)	3 (5.00%)	Z= 0.3895, P=0.6965
Duration of illness	12.46 $\pm$ 4.12	11.65 $\pm$ 4.71	P=0.3063
Comorbid patients	18 (30.00%)	22 (36.67%)	Z=0.7746, P= 0.4413
Number of patients on Oxygen Support	42 (70.00%)	35 (58.33%)	Z=1.3326, P= 0.1835
Inhaled FiO2	40.25 $\pm$ 12.26	43.24 $\pm$ 13.01	P=0.1976
Alleviation of COVID-19 related symptoms	5 (8.33%)	13 (21.67%)	Z=2.045, P=0.0403
Cessation of Cough			
<3 Days	20 (33.33%)	9 (15.00%)	Z=2.59, P=0.0096
3-7 Days	35 (58.33%)	22 (36.67%)	Z=2.376, P=0.0173
7-14 Days	4 (6.67%)	21 (35.00%)	Z=3.821, P=0.0001
>14 Days	1 (1.67%)	8 (13.33%)	Z=2.426, P=0.0151
Average duration to stop cough	4.85 $\pm$ 3.94	7.68 $\pm$ 5.43	P=0.0014
Average Duration of Oxygen support	5.21 $\pm$ 4.23	7.82 $\pm$ 6.35	P=0.0092
Duration of Hospital Stay	6.54 $\pm$ 4.87	8.87 $\pm$ 6.12	P=0.0284
COVID-19 related mortality	0 (0.00%)	1 (1.67%)	Z= 1.004, P=0.3173

clinically moderate to severe patients COVID-19 required oxygen support as a part of COVID management. Average time duration for which patients required oxygen support was found to be lesser (5.21 days) in patients treated with steroids as compared control group (7.82 days) which did not expose with inhaled steroids ( $P=0.0092$ ). Meantime duration of hospitalization after onset of cough was found to be significantly lesser (6.54 days) in patients treated with inhaled steroids as compared to control group (8.87 days) ( $P=0.0284$ ). COVID-19 related mortality was not significantly differing among both groups.

**Graph 1: Time duration for resolution of Cough in cases and control groups**



**Discussion:**

In this study, we evaluate the effectiveness of inhaled steroids in the treatment of persistent cough after COVID-19 infection. We also try to establish an association between use of inhaled steroids and recovery from post COVID Cough. This is a retrospective case-control observational study that includes an age-matched, gender-matched, disease severity matched and underlying chronic medical illness matched control group in order to avoid these confounding factors for pneumothorax. Explaining the exact association between COVID-19 and post COVID cough is more challenging.

In this study, we found that the inhaled glucocorticoid budesonide, given for the persistent cough, might be an effective treatment for post infectious cough in COVID-19 infected patients. Inhaled budesonide is a simple, safe, well studied, inexpensive, and widely available treatment. This is also significantly helpful in low-income and middle-income countries where the majority of currently approved COVID-19 treatments are unlikely to ever reach patients as a consequence of variable health-care systems<sup>(17)</sup>. Although systemic steroids are well documented for treatment of moderate to critical COVID-19 infection but their role is not approved for use in post infectious cough. Furthermore, inhaled budesonide could work as an adjunct to reduce pressure on health-care systems and symptomatically to felt better to patients. In this study, our eyes focused on inhaled budesonide because of the unexpected an under-representation of persistent cough in patients with asthma and COPD with severe COVID-19<sup>(18)</sup>. The common therapy between these lung diseases is inhaled glucocorticoids, either as a mono, dual, or triple constituent. Furthermore, inhaled glucocorticoids are among the most prescribed medicines of any class around the world, listed by the WHO as essential medicines.

In this study, both groups have matched age profile, gender profile, disease severity, window period for post infectious cough, comorbid status and required oxygen support in order to avoid these confounding factors which influence recovery from post infectious cough. We found that few COVID-19 infected patients of study group deteriorate in the course of disease management. The alleviation of COVID-19 related symptoms was found to be significantly lesser in patients treated with inhaled steroids as compared to patients not used inhaled steroids for persistent cough. Hence, inhaled steroids also protective to prevent further progression of COVID-19 disease. Outcome of study treatment judged by the length of time the cough was stopped. Average time duration to relieve from this disabling symptoms in cases treated with inhaled steroids was significantly lesser than in control group. Post COVID persistent cough relieved early in patients treated with inhaled steroids as compared to control group. Among patients treated with inhaled steroids, more than 92% patients relieved from cough within one week while in control group only 52% patients relieved from cough within one-week duration ( $P < 0.05$ ).

S Ramkrishanan et al in their study suggest that intervention with an inhaled glucocorticoid might affect rate of the persistent long-term symptoms in COVID-19 (long COVID); and should be investigated further in view of the considerable long-term health and economic impact of long COVID. There are several open-label studies currently open to recruitment examining the role of inhaled budesonide in COVID-19 infection (ISRCTN86534580, NCT04355637, NCT04331054) and others investigating the role of inhaled ciclesonide (NCT04330586, NCT04377711, NCT04381364, NCT04356495); whether these studies also show an effect on long COVID will be of importance. As per ICMR guidelines, clinically moderate, severe and critical patients of COVID-19 required oxygen support as a part of COVID management. Average time duration for which patients required oxygen support was found to be significantly lesser in patients treated with steroids as compared control group which did not expose with inhaled steroids. The average time duration of hospitalization after onset of cough was found to be significantly lesser in the patients treated with inhaled steroids as compared to control group. Hence, COVID-19 infected patients treated with inhaled budesonides recovered early from progressive COVID-19 disease.

**Conclusion:**

Our study highlights use of inhaled budesonides as a treatment persistent post COVID cough. After COVID infection, persistent cough may be result from continuous inflammatory activity in respiratory tract. This study concluded that the inhaled budesonide along with standard of care treatment helpful to relieve post COVID persistent cough. Beside early relief in cough, inhaled steroids also useful in early withdrawal of oxygen and early discharge from hospital. So it reduces healthcare burdens and patient's anxiety.

**Limitation:** There are several limitations in this study. The number of patients was limited and needs to have been studied on a larger patient cohort. It is an observation study and case findings might be associated with individual characteristics.

**Ethical approval:** This study approved by ethical and research committee of SMS medical college and Hospital, Jaipur, India.

**Author contributions:** S. Bhandari and G. Rankawat formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; G. Rankawat and A. Singh collected and analyzed data for study. G. Rankawat writes the manuscript. S. Bhandari and conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not for profit sectors.

**Availability of data and materials:** Available from corresponding author upon reasonable request.

**Declaration of competing interest:** All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

**References:**

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382: 1708–20.
3. Thorlund K, Dron L, Park J, Hsu G, Forrest JI, Mills EJ. A real-time dashboard of clinical trials for COVID-19. *Lancet Digit Health* 2020; 2: e286–87.
4. Rosendal M, Carlsen AH, Rask MT, Moth G. Symptoms as the main problem in primary care: a cross-sectional study of frequency and characteristics. *Scand J Prim Health Care*. 2015;33(2):91–9.
5. French CT, Fletcher KE, Irwin RS. A comparison of gender differences in health-related quality of life in acute and chronic coughers. *Chest*. 2005; 127(6):1991–8.
6. Kardos P, Berck H, Fuchs KH, Gillissen A, Klimek L, Morr H, et al. Guidelines of the German Respiratory Society for diagnosis and treatment of adults suffering from acute or chronic cough. *Pneumologie*. 2010;64(11):701–11.
7. Braman SS. Postinfectious cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 Suppl):138–46.
8. Bardin PG, Fraenkel DJ, Sanderson G, Lampe F, Holgate ST. Lower airways inflammatory response during rhinovirus colds. *Int Arch Allergy Immunol*. 1995;107(1–3):127–9.
9. Trigg CJ, Nicholson KG, Wang JH, Ireland DC, Jordan S, Duddle JM, et al. Bronchial inflammation and the common cold: a comparison of atopic and non-atopic individuals. *Clin Exp Allergy*. 1996;26(6):665–76.
10. Ponsioen BP, Hop WC, Vermue NA, Dekhuijzen PN, Bohnen AM. Efficacy of fluticasone on cough: a randomised controlled trial. *Eur Respir J*. 2005;25(1): 147–52.
11. Pornsuriyasak P, Charoenpan P, Vongvivat K, Thakkinstian A. Inhaled corticosteroid for persistent cough following upper respiratory tract infection. *Respirology*. 2005;10(4):520–4.
12. Nicolau DV, Bafadhel M. Inhaled corticosteroids in virus pandemics: a treatment for COVID-19? *Lancet Respir Med* 2020; 8: 846–47.
13. Matsuyama S, Kawase M, Nao N, et al. The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex in cultured cells. *J Virol* 2020; 95: e:01648-20.
14. Peters MC, Sajuthi S, Deford P, et al. COVID-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids. *Am J Respir Crit Care Med* 2020; 202: 83–90.
15. Johnstone KJ, Chang AB, Fong KM, Bowman RV, Yang IA. Inhaled corticosteroids for subacute and chronic cough in adults. *Cochrane Database Syst Rev*. 2013;(3):CD009305. <https://doi.org/10.1002/14651858.CD009305.pub2>.
16. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
17. Tan-Torres Edejer T, Hanssen O, Mirelman A, et al. Projected health-care resource needs for an effective response to COVID-19 in 73 low-income and middle-income countries: a modelling study. *Lancet Glob Health* 2020; 8: e1372–79.
18. Skevaki C, Karsonova A, Karaulov A, Xie M, Renz H. Asthma-associated risk for COVID-19 development. *J Allergy Clin Immunol* 2020; 146: 1295–301